Analysis of factors that help to predict malignancy in patients with thyroid nodules presenting to the General Surgery Out- patient department in Christian Medical College, Vellore.

A dissertation submitted to the Dr. M.G.R. Medical University, Tamil Nadu; in partial fulfilment of the requirement for the M.S. branch I (General Surgery) examination to be held in April 2013.

Certificate

This is to certify that the dissertation entitled "Analysis of factors that help to predict malignancy in patients with thyroid nodules presenting to the General Surgery Out- patient department in Christian Medical College, Vellore**"** is a bonafide work done by Dr. Vimalin Samuel, post graduate Resident in Masters of General Surgery 2010-2013 at the Christian Medical College, Vellore, towards partial fulfilment for the MS General Surgery-Branch 1 final Examination to be held in April 2013.

Signature:

Guide:	**Head of the Department:**	**Principal**
Dr M.J PAUL, Professor and Head, Dept of Endocrine Surgery, Christian Medical College, Vellore.	Dr. Benjamin Perakath Professor and Head, Dept of Surgery, Christian Medical College, Vellore.	Dr. Alfred Job Daniel Professor, Dept of Orthopedics Christian Medical College Vellore

ACKNOWLEDGEMENT

This dissertation would be incomplete without expressing my gratitude to those who were involved in its conception and completion.

I thank my guide, Dr. M.J. Paul, Professor of Endocrine Surgery, CMC, Vellore, for his continuous support and guidance.

I thank Dr. Aravindan Nair, retired head and honorary Professor of Endocrine Surgery, for his help and ideas in setting up my study.

My thanks to my co-guide, Dr. Sheila Nair, Professor of Pathology, CMC Vellore for the help extended in appropriate reporting of the FNACs.

My thanks to my co-guide, Dr. Aparna I, Department of Radiology for help in interpreting the thyroid ultra sound.

My thanks to my co-guide, Dr. Anuradha M, Department of Radiology for help in interpreting the thyroid ultra sound.

I thank my parents for their support and encouragement.

Above all I thank God for His grace and guidance.

TABLE OF CONTENTS

S. No.	***TITLE***	PAGE NO.
1	Abstract	5
2	Introduction	6
3	Relevance of the study	7
4	Aim and Objectives	8
5	Review of literature	9
6	Methods	56
7	Results	58
8	Discussion	71
9	Conclusion	74
10	Limitations	75
11	Consent form	76
12	Patient information	77
13	Performa	78
14	Bibliography	80
15	IRB form	82

ABSTRACT

TITLE OF THE ABSTRACT:

Analysis of factors that help to predict malignancy in patients with thyroid nodules presenting to the General Surgery Out- patient department in Christian Medical College, Vellore.

DEPARTMENT: **Endocrine Surgery, CMC Vellore**

NAME OF THE CANDIDATE: **Vimalin Samuel**

DEGREE AND SUBJECT: **MS (General Surgery)**

NAME OF THE GUIDE: **Dr. M.J Paul**

OBJECTIVE :

To study and analyse the factors that help to predict malignancy in patients with thyroid nodules presenting to the General Surgery Out-patient department in Christian Medical College, Vellore.

INTRODUCTION:

Thyroid nodules are considered common , as they are found in more than 7 percent of the adult population. However, this incidence goes up even higher if ultra sound is used as a screening tool.

Among patients presenting with thyroid nodules, 5%–15% will be malignant depending upon age, sex, radiation exposure history, family history and other factors.(1)

Differentiated thyroid cancer (DTC), which includes papillary and follicular cancer, comprises of the vast majority(90%) of all thyroid cancers. The increasing level of detection may be due to the increasing patient awareness, use of neck ultrasonography and early diagnosis and treatment. These are the trends that are changing the initial treatment and follow-up for many patients with thyroid cancer.

The difficult bit is in identifying the thyroid nodules that are malignant and the challenge to the surgeon lies in deciding which nodules require surgical excision.

RELEVANCE:

The incidence of thyroid swellings vary from place to place depending upon which area of India, the patient is from. In a tertiary care centre, like Christian Medical College, Vellore, thyroid nodules are a common problem because of referrals from a wide geographical source with a significant number from the " goitrogenic belt" of India. In this situation, it becomes very important to have a clear idea of the risk factors for malignancy so that the doctor can offer an appropriate course of treatment for the patient and the patient is also able to make an informed decision. Most of the literature and guidelines that are available have been based on studies that been conducted on western population. Does the same hold good for the Indian population?

AIMS AND OBJECTIVES:

In patients presenting with any nodule of the thyroid, to assess with clinical criteria, Ultra sound neck and FNAC so as to predict the likelihood of malignancy:

a) using a triple assessment , consisting of:

   - history and examination

   - FNAC of the nodule

   - ultra sound neck.

b) Predict the percentage likelihood of nodules diagnosed as non-malignant on FNAC, to be malignant on histopathology.

c) To look also at independent risk factors, in ultra sound and FNAC for diagnosis of malignancy.

d) To form a treatment protocol based on triple assessment for any thyroid nodule.

Literature review:

CLINICAL EVALUATION OF THYROID NODULES:

The evaluation of a patient with a thyroid nodule consists of three arms; a good history and general examination, ultrasonography of the gland and fine needle aspiration cytology of the nodule.

History and clinical examination:

There is no doubt that first and foremost, for an evaluation of a thyroid nodule, a detailed history and thorough clinical examination will lead the way to a sound diagnosis.

Patients usually present with a large palpable nodule in the neck incidental nodule found on imaging studies . Some palpable nodules may not correspond to radiological abnormalities.

Non palpable nodules that are detected on ultra sound or other anatomic imaging studies, usually as part of evaluation for other reasons are called incidentally discovered nodules or ‘‘incidentalomas’’. Non palpable nodules have a similar risk of malignancy as palpable nodules that are of the same size(2).

Generally, only the nodules that are >1 cm in size should be evaluated, as they have significantly higher risks of malignancy(2).

There are some nodules which are <1 cm in size that may require complete evaluation when suspicious ultra sound features, associated palpable lymphadenopathy or previous history of radiation to head or neck or history of thyroid malignancy in first-degree relatives(2).

However, in a recent study by Burch HB, Shrestha M, Crothers BA, they analysed Whether the size of the nodule plays a role in predicting malignancy.

During a ten year period (2001 to 2011), 3013 patients had fine needle aspirations of thyroid nodules at the Walter Reed Army Medical Center(3). The patients who underwent subsequent thyroid surgery were included in the analysis(3). The nodule size was assessed by ultrasound measurement of the largest diameter and categorized as 0.5 to 0.9 cm (group A), 1.0 to 3.9 cm (group B) and ≥4 cm (group C)(3).

FNA cytology was categorized by the Bethesda System for Reporting Thyroid Cytopathology: benign, atypia (follicular lesion of undetermined significance), follicular neoplasm, suspicious for malignancy, or malignant. All categories except for benign were considered positive for calculation of the sensitivity and specificity of the F

NA. There were 35 nodules in group A, 533 nodules in group B and 127 nodules in group C. The malignancy rate based on surgical pathology was 18.6% (129 of 695 nodules) and did not differ among the size categories.

The malignancy rate was 23% in both men and women. (3) So this leads us back to the question of whether size matters? Traditionally, the teaching has been that, nodules greater than 4cm are at high risk for malignancy.

However with the advent of imaging and detection of smaller cancers, size does not appear to be a risk factor. The most pronounced environmental risk factor for thyroid cancer is exposure to ionizing radiation. Ionizing radiation is either due to medical treatment (childhood radiation therapy for benign or malignant disease, adult treatment of malignancies) or nuclear fallout (atomic bomb / testing survivors, nuclear energy accidents).

Ionizing radiation may exert this effect through several changes to the cell, includingGenomic instability. The effects of ionizing radiation are most pronounced in children, especially those younger than 10 years old at the time of exposure. The latency Period of developing cancer from this exposure is approximately 10 years for patients.

Having external beam radiation exposure to less than 5 years for victims of the Chernobyl accident and the increased risk persists for 30 to40 years. Exposure to Ionizing radiation has been shown to increase the risk of malignancy for a thyroid Nodule to 30% to 40%. Furthermore, this risk of malignancy is increased regardless of nodule number and size and multifocal malignancy is found more than half of the time. A history of prior radiation exposure mandates initial total thyroidectomy.

The gender-specific distribution is equal in those older than 65 and given that overall two-thirds of cancer cases are women, there would seem to be a link between reproductive hormones and the development of thyroid cancer. Estrogen has been linked as a stimulus for genomic instability and this may be how it exerts its mutagenic effects on the thyroid. Studies have yet to conclusively link traditional carcinogens such as alcohol and tobacco to the development of well differentiated thyroid cancers. Data are conflicting as to what role iodine - rich versus iodine - deficient diets play in the development of thyroid cancer.

Countries with iodine-rich diets such as the United States and Sweden have slightly increased incidence of papillary cancer and countries with iodine-deficient diets such as Switzerland and Australia have slightly increased incidence of follicular thyroid cancer.(4)

A dominant or solitary nodule is more likely to represent carcinoma than a Multi nodular gland with an incidence of malignancy from 2.7 to 30% and 1.4 to 10% respectively(1). Yet, the overall risk of malignancy within a gland with a solitary nodule is approximately equal to that of a multi nodular gland due to the additive risk of each nodule . Important elements in the patient's history which increase the likelihood of malignancy include reports of rapid growth, dysphagia, dysphonia, male gender, presentation at extremes of age (less than 20 years or more than 70 years) and a family history of medullary thyroid carcinoma or multiple endocrine neoplasia(1) .

Patients must be asked for any family history of either benign or malignant thyroid diseases. Although not well defined, there most certainly exists a genetic component to thyroid cancers. In fact a family history of thyroid carcinoma may increase an individual's risk 3-fold when a parent has the disease and up to 6-fold if a sibling has the disease.(4)

The familial medullary thyroid cancers, multiple endocrine neoplasia 2, The familial papillary thyroid tumours, familial polyposis coli, Cowden disease, Gardner's syndrome even though they are not common, must be considered.(5).

Papillary thyroid cancers and follicular thyroid cancers have distinct genomic and proteomic signatures. Pathways are now emerging that demonstrate how these differences play a role in governing tumor biology. Mutations that involve RET, NTRK1, BRAF, PPARγ, or Ras can be detected in almost 70% of cases. There are at least 12 different RET mutations, known as PTC/Ret chimeric onco proteins, which seem to be an early event in thyroid tumorigenesis,

with series showing a high prevalence in papillary micro carcinomas and also a high proportion of the post-Chernobyl childhood-induced papillary thyroid carcinomas.

BRAF mutations are seldom found in radiation-induced cancer. These mutations are postulated to produce a more aggressive phenotype of papillary cancers as they are found in many of the more poorly differentiated subtypes. Follicular carcinomas have mutations in PPARγ (rarely found in papillary cancers), AKT pathways, and Ras.

Symptoms like difficulty in breathing, neck tenderness, pain, difficulty in swallowing or even change in voice can be attributed to thyroid problems, but in many patients, these symptoms are due to non thyroid diseases. In those patients that are symptomatic, evaluation must start with getting a proper history, doing a full physical examination, reassuring the patient and for choosing the correct laboratory tests.

Acute pain is most often because of hemorrhage in to a nodule that is cystic in nature. However, patients that present with rapid increase in size of the thyroid nodule, lymphoma or anaplastic carcinoma of thyroid must be considered.

The beginning and slow progress of neck symptoms and signs are usually because of compression of the structures in the neck and upper chest cavity (oesophagus and trachea), which happens in those thyroid nodules that are found in large goiters.

The features of compression are not so common and are found in the elderly or middle-aged having a long - standing multi nodular goitre. The goiter that is growing downwards into the superior mediastinum can result in partial or complete obstruction of the chest inlet, causing venous obstruction. When the patient is made to raise his or her arms above the head ; i.e. Pemberton's sign, more narrowing of the chest inlet is produced which is followed by over filling of the external jugular veins and facial congestion.

If this is seen when there is a smaller goiter, the features of tracheal compression. May suggest an underlying cancer. Differentiated thyroid cancers will usually not cause airway obstruction or vocal cord palsy or oesophageal problems but even if there are no symptoms, it does not rule out malignancy.(5)

Physical examination:

Physical exam findings that increase the concern for malignancy include:

• Nodules that are larger than 4 cm in size (19.3% risk of malignancy)

• Firmness to palpation

• Fixation of the nodule to adjacent tissues

• Cervical lymphadenopathy

However, these findings are very often limited by certain factors such as the patient's body habitus, as well as an inherent variation between physicians and their assessment of nodules so much so that precise measurement using imaging is a must of evaluation of a thyroid nodule.(1)

A hard nodule is suspicious as traditionally goitre has always been described as firm. However a benign multi nodular goitre may turn hard because of calcifications or hemorrhage.

Fixity of a nodule is because of its infiltration into surrounding structures. This feature is seen in malignant thyroid nodules and fixed swelling almost always require excision.

Cervical lymphadenopathy in the Ipsilateral level 3 or 4 is the most specific pointer to malignancy in a thyroid nodule; rarely this may prove to be red herring as in a patient with a thyroid swelling, they may have associated reactive hyperplasia of a the corresponding draining lymph nodes especially in the presence of autoimmune thyroiditis. However, it is essential to assess these lymph nodes with an ultra sound of the neck and plan the surgery with an option of doing a neck dissection with a frozen section of the lymph node if necessary.

Role of biochemical evaluation in thyroid nodules:

The initial investigation that is necessary for all the patients presenting with a clinically palpable solitary lesion is an assessment of the biochemical properties of the thyroid gland as clinical examination in itself is not enough to establish thyroid dysfunction(6). A low level of serum thyroid stimulating hormone will forewarn the clinician of the possibility that the solitary lesion clinically found may be a toxic nodule.

The workup proceeds with total or free thyroxine (T4) and total tri iodothyronine (T3) to better evaluate the hyper thyroid state. This occurs in approximately 10% of patients with a solitary thyroid nodule and is suggestive of a benign hyper functioning adenoma(1). On the other hand, it may even be part of a toxic multi nodular goitre or it may be a solitary nodule in a case diagnosed with Grave's disorder.

FNAC should be avoided as an 'atypical' result in biopsy may be reported due to the hyper cellularity that is often associated with lesions that function autonomously. A radionuclide scan is considered as the investigation of first choice(6).

Toxic multi nodular goiters may however harbour both hyper functioning and cold regions. Thyroid nodules in those with Graves' s are usually found as malignant in around 9% of the cases(5).

Ultrasonography(US)

Ultrasonography has proved to be the imaging of choice for thyroid nodules. It can identify nodules that are too small to be palpated, the presence of multiple nodules, central, or lateral neck lymphadenopathy and also provides an accurate measurement of nodule diameter for interval monitoring.

Fujimoto et al in 1967 were the first to describe detection and characterization of thyroidnodules by US. From then on, several studies have been designed in order to establish the validity of thyroid ultra sound in making a diagnosis of either a benign or a malignant thyroid nodule.

Moreover, the rapid development of ultra sound equipment during recent years, with the availability of 7–13-MHz high-frequency transducers, has allowed the detection of very small thyroid lesions (2–3 mm)(7). Non - palpable thyroid nodules are detected by ultrasound in 13–50% of the general population.

Thyroid ultrasound features that are most commonly found in malignant thyroid nodules are Micro calcifications, hypo echogenicity, absent halo or irregular margins, solid lesions, intra nodular vascularity and the nodule that is taller than wide. These features, if taken by themselves alone, are very poor predictors of malignancy. However if they are described together, the specificity will go up at the cost of sensitivity(7).

To visualize the thyroid gland optimally, the patient is placed in the supine position with a Pillow underneath the shoulders to extend the neck slightly, allowing the head to rest on the examination table.

In older patients or those who have degenerative changes in the neck, small towels can be placed under the head to the level where the patient is most comfortable while still allowing access to the neck. The thyroid gland is then imaged in transverse and longitudinal views with a high frequency (10–15 MHz) linear transducer. The highest frequency is used while still allowing adequate sonographic penetration.

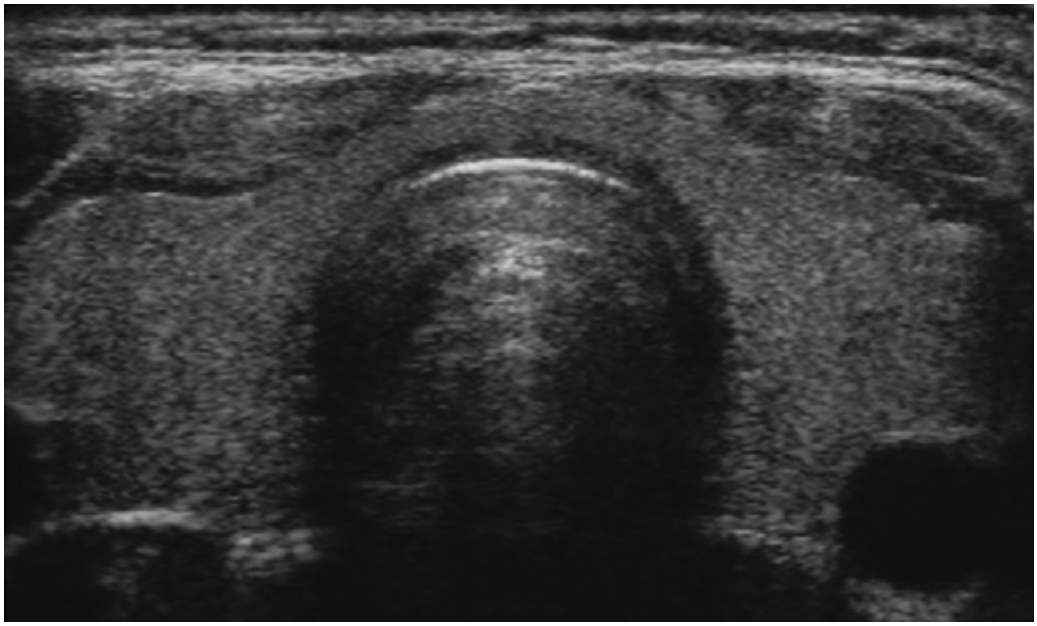
A thyroid nodule on US is defined as a region of parenchyma that is sonographically distinct from the remainder of the thyroid and located within the confines of the echogenic thyroid apsule. When a nodule is detected, its size should be measured in three dimensions and the location within the thyroid gland (upper pole, mid-gland, lower pole, right or left) should be noted by the sonographer.

Nodule size:

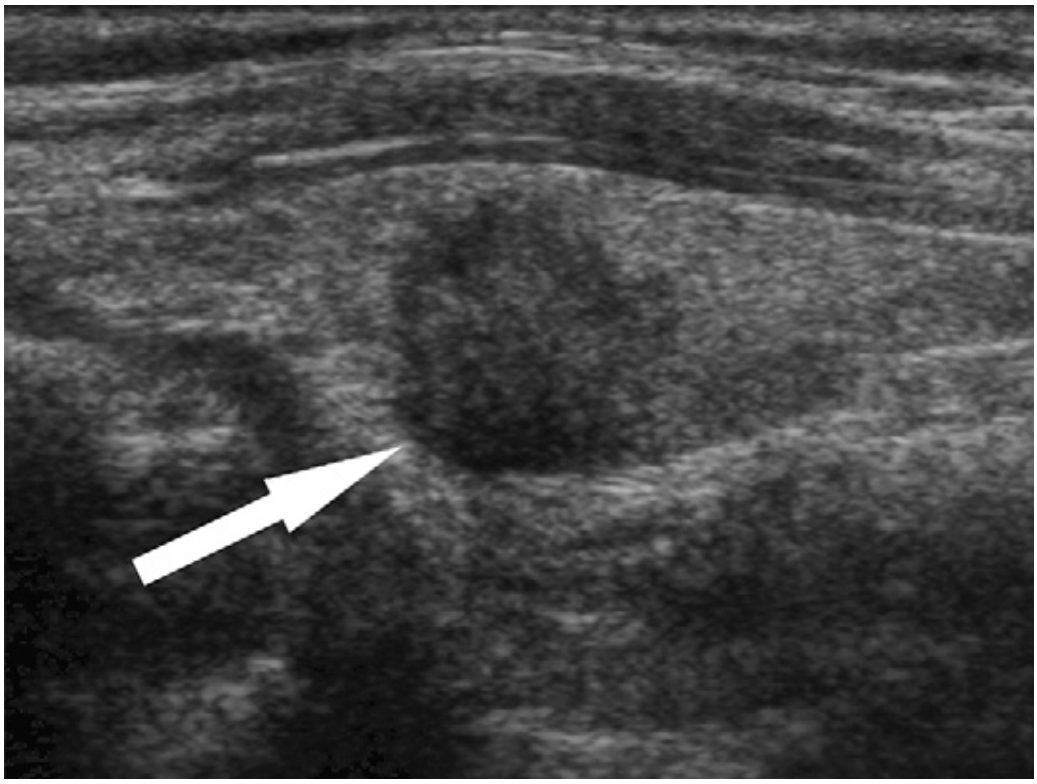
Inspite of extensive research, the worldwide consensus is that, most ultra sound features of malignancy applies to nodules that are greater than 1cm in size. Although the American Association of Clinical Endocrinologists and American Thyroid Association guidelines continue to use 1 to 1.5 cm as a practical threshold for selecting nodules for FNA, it has been shown that size is not a good predictor of malignancy(8).

Hypoechogenicity:

An echogenic appearance is commonly associated with follicular neoplasms, both benign and malignant, but can also be seen in papillary cancers. ‘‘Marked hypoechogenicity’’ is defined as echogenicity less than that of adjacent musculature, is a more specific appearance for thyroid carcinoma, but this feature has a fair amount of inter observer variation.(8)



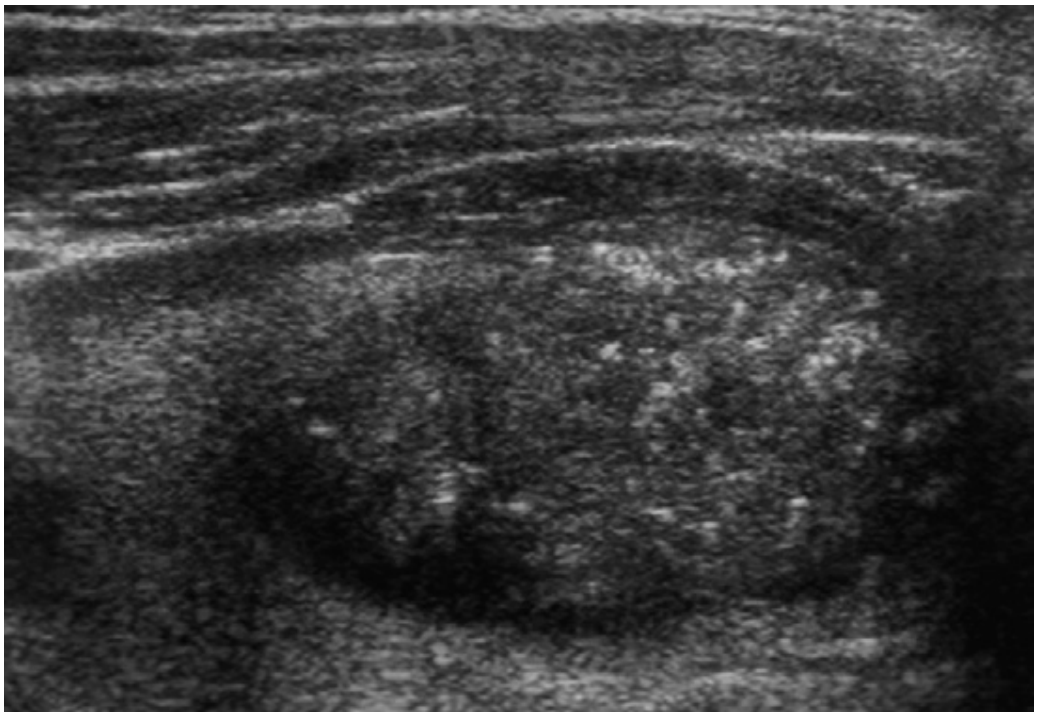
Transverse gray-scale mode image of a normal thyroid gland, which is uniformly echogenic relative to overlying strap musculature.(9)



Longitudinal image of hypo echoic papillary cancer (arrow) with irregular margins.(9)

Calcification:

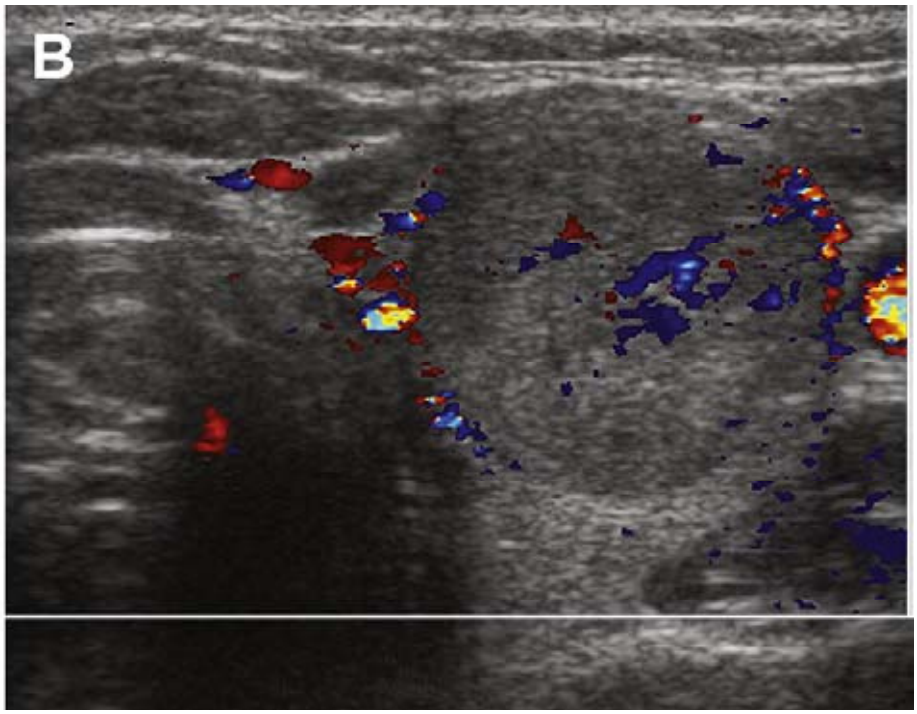
Calcifications have been found in papillary, medullary, and anaplastic thyroid carcinomas as either psammoma bodies or as amorphous granular deposits. Of all the sonographic features associated with thyroid malignancy, micro calcifications are the most specific. Micro calcifications are defined as punctuate echogenic foci without acoustic shadowing or associated comet-tail artifact. The positive predictive value of a finding of microcalcifications in a thyroid nodule ranges from 24.3% to 70%.(7)



Transverse image of right thyroid lobe in papillary cancer which shows innumerable. Micro calcifications create a ‘‘snowstorm’’ appearance.(9)

Vascularity:

Almost all solid nodules display some flow on colour Doppler interrogation with current generation Ultrasound equipment. In general, a peripheral flow pattern tends to be a feature of benign nodules and malignant nodules tend to have internal vascularity, but there is considerable overlap. Although marked internal vascularity was more often present in malignant than benign nodules, more than half of nodules with internal hyper vascularity were benign(7).



Transverse image shows flow in peripheral hypo echoic capsule and internal vascularity.(9)

Composition:

Every nodule must be assessed with the percentage of nodule which is found to be solid against the percentage of the nodule that is found to be cystic. Lesions may be categorized semi quantitatively, depending upon the fraction of cystic and solid components. This can also be done using descriptive terminology that is found on the pre dominant composition ie: solid, pre dominantly solid or mixed solid with cystic or pre dominantly cystic with cystic.

The nodules that are solid or mostly solid have a greater risk of turning out to be malignant than the mixed or pre dominantly cystic type of nodules. The nodules that are found to be cystic or mostly cystic have a low risk of malignant potential. Lesions that have a mixed composition have been found to have a lower risk of malignancy(8).

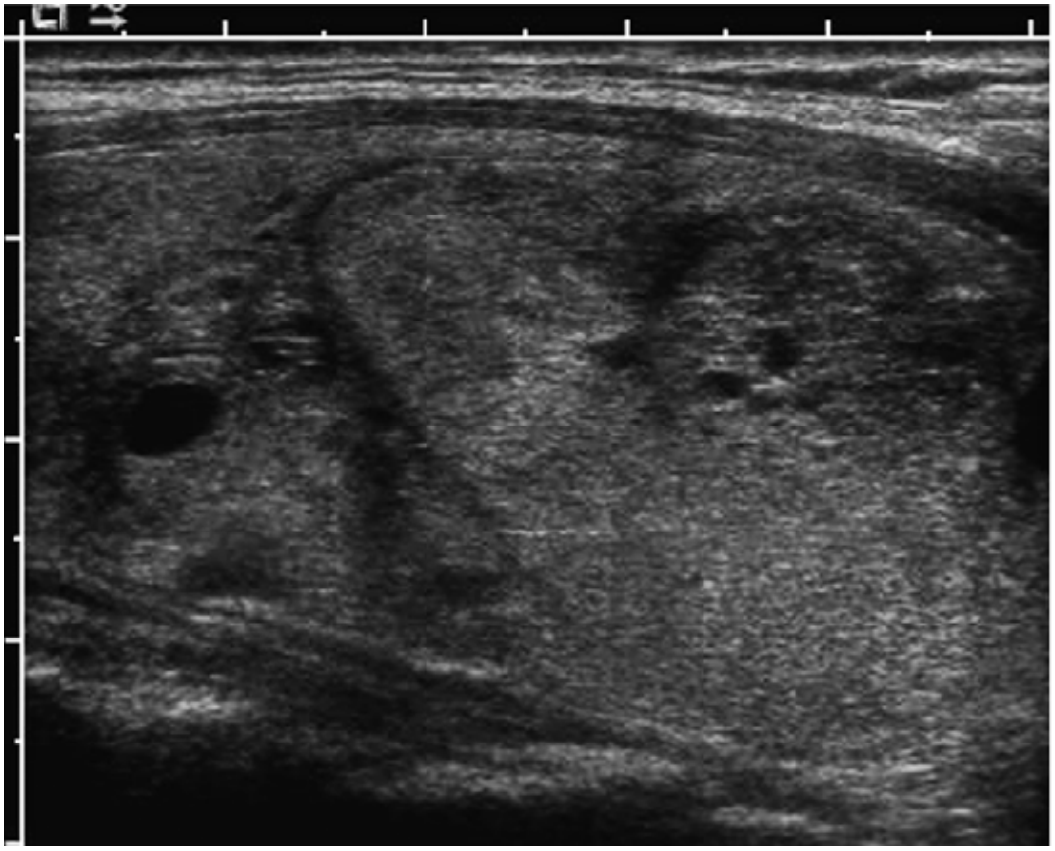


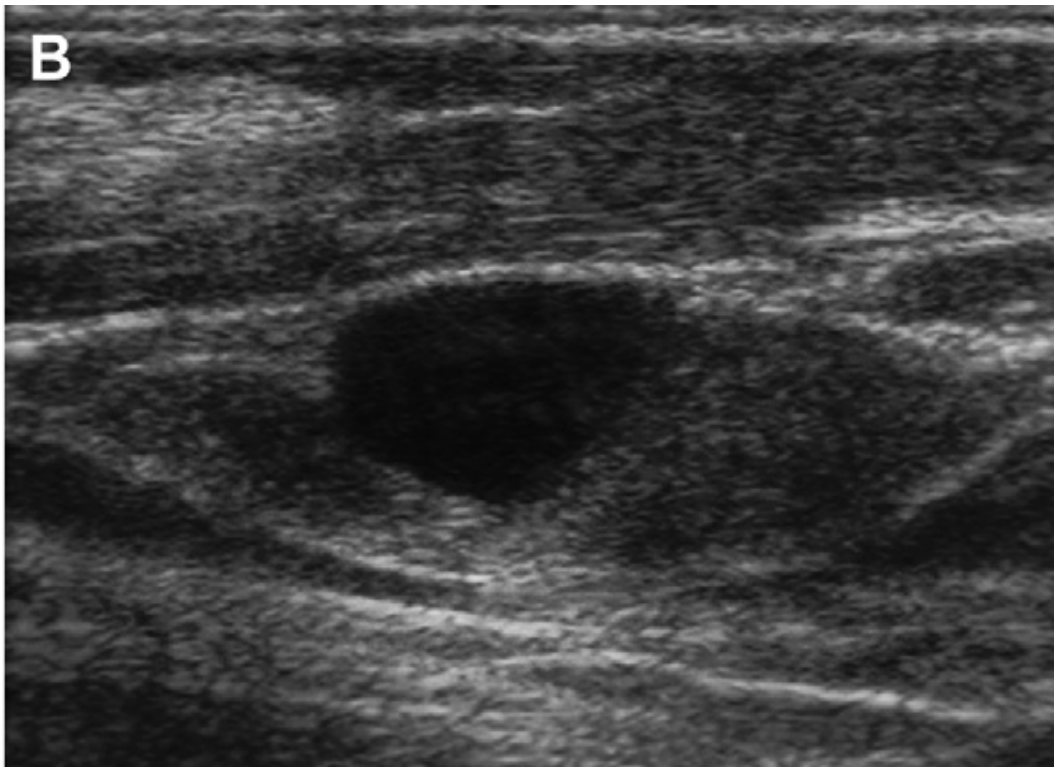
Image obtained with conventional high resolution transducer shows small cystic areas in lower portion of nodule.(9)

Height of the nodule:

By analogy with breast carcinomas, some studies have shown that a shape taller than wide was 92.5% specific for malignancy. This feature had fairly low (32.7%) sensitivity. However, this finding was not definitively confirmed in all series(7).

Abnormal cervical lymph nodes:

Ultra sound evaluation of any lymph node will depend upon on its vascularity, shape, sizeand architecture. The ultra sound markers of cancer are echotexture that is heterogenous, areas of calcifications and areas of cystic change within the node. A round node or a node that causes mass effect is at a higher risk of turning out malignant. Generally, the nodal size is not a very reliable indicator for malignant change in a node than the shape and the architecture, even though the risk of the node being malignant increases when the size of the node increases. Hence, any node must be looked upon with suspicion if they are found to be greater than 7mm in the short axis or if there is loss of fatty hilum(7)(8).



Longitudinal image of metastatic papillary carcinoma with cystic change in cervical lymph node.(9)

Recent advances:

Ultra sound evaluation of the thyroid nodule has recently under gone a sea of change with the introduction of the TIRADS score. Horvath and his collegues made six groups and named it the Thyroid Imaging Reporting and Data System (TIRADS) which were founded on ten ultra sound patterns.

They then calculated the frequency of cancers in every group: 0% in TIRADS 1 and 2, <5% in TIRADS 3, 5% to10% in TIRADS 4A, 10% to 80% in TIRADS 4B and >80% for TIRADS 5. They then went on to suggest that patients with nodules rated TIRADS 4 and 5 must have biopsies(10). Their results showed a high power of discrimination however the validity of the study has not yet been confirmed.

In April 2012, Cheng SP, Lee JJ, Lin JL, Chuang SM, Chien MN, Liu CL from the Surgical department of Mac kay Memorial Hospital in Taiwan, in the Institute of Pharmacology at the Taipei Medical University in Taiwan published their results including 498 nodules in 437 patients that went on to have thyroidectomies. Two surgeons with two endocrinologists separately reviewed the sonology images. The main reason for this study was to assess the inter - observer variability along with the accuracy.

A moderate to substantial inter observer agreement was found for the final assessment Group that was kappa = 0.6. The results showed that the sensitivity and specificity and negative predictive value were 94 percent, 43 percent and 96 percent each. The positive predictive values in the groups 4 and 5 were 32 percent and 60 percent each. The calculated sensitivity came to 92 percent, 99 percent, 96 percent and 89 percent. The specificity calculated was 25 percent, 37 percent, 41percent and 62 percent for tumour sizes of <2 cm, to 3, 3 to 4 and >4 cm, respectively.

They concluded that the TIRADS is useful but definitely not the most optimal tool used for reporting in thyroid swellings. They also felt that the size of the tumour has an important role to play in inter - observer agreement and performance in diagnosis.

The role of thyroid elastography is being investigated as a modality of investigation for the thyroid gland. The basic principle of elastography is that tissue compression produces strain

(displacement) within the tissue that which is found to be small in hard than in soft tissues, and is then scored by measuring the amount of distortion that is produced by the beam of ultra sound after applying an external force(8).

The principle of ultra sound elasto graphy is to see two ultrasonographic pictures, before and after the tissue is compressed by the probe and to see tissue displacement when the beam propagates(9). The combined auto correlation method dedicated software is programmed to give an accurate measurement of the distortion of tissues.

The Ultra sound elastography image is matched with an elasticity colour scale and classified by using the elasticity score of Ueno and co-workers.(9)

Score	
 1	Elasticity in the whole nodule
 2	Elasticity in a large part of the nodule
 3	Elasticity only at the peripheral part of the nodule
 4	No elasticity in the nodule
 5	No elasticity in the nodule and in the posterior shadowing

Elasticity score (9)

The predictivity of Ultra sound elastography was shown to be independent of the nodule size, with high sensitivity and specificity being observed also in nodules < 1 cm, independently from the position of the nodule within the thyroid lobe(9). Available data suggest that ultra sound elastography is the best available non-invasive tool for the evaluation of thyroid nodules, comparable to fine needle aspiration.

Radioisotope imaging

Radioisotope scanning has been used to determine whether a thyroid nodule is functioning. However, it does not provide an accurate measurement of size. The radioisotopes that have been used are technetium (99mTc), I 123 and I 131 and although the same information is obtained with similar amounts of radiation exposure, radioiodine is the preferred option. Of these, about 80 to 85% of thyroid nodules are cold and about 10% of these nodules are malignant. The hot nodules account for 5% of all nodules and the likelihood of malignancy is less than 1% for these nodules. Everything put together, the sensitivity for the diagnosis of thyroid cancer is 89 to 93%, specificity is 5%, and the positive predictive value of malignancy is only 10. The use of radioisotope for performing thyroid scans has been nearly abandoned in the initial workup of a thyroid nodule.

Computed tomography (CT) and magnetic resonance imaging (MRI)

Both of these modalities have almost no role in evaluation of any thyroid swelling and are very rarely indicated in the initial workup. However, they both have excellent (100% sensitivity) for evaluating the extent of large sub sterna or retrosternal goitres which may be compressing or infiltrating nearby structures(1). It is imperative to note that iodinated contrast material utilized for routine CT scans prevents scintigraphy or administration of radioactive iodine (1) therapy for atleast a period of 1 to 2 months and is avoided where early ablation may be required. Gadolinium contrast used with MRI does not interfere with thyroid uptake of radiotracer, but it is significantly more expensive than CT or ultrasound(1) MRI images are also of low contrast, making it difficult for surgeons to interpret and use as a roadmap for a difficult procedure.

18F-fluorodeoxyglucose positron emission tomography-computed tomography (18FDG-PET/CT)

18FDG-PET/CT is being used extensively in oncology for staging, evaluation of treatment response and detecting recurrences on the principle that malignant cells have a higher uptake of 18 FDG due to increased metabolic demands in comparison to normal tissues. In general, the appearance of the images and maximum standard uptake value (SUV max) can be used to differentiate between malignant and benign lesions. This does seem to hold good for thyroid nodules as there is no significant difference in the SUV max between benign and malignant 18FDG - avid nodules(1).

The role of 18FDG - PET/CT in reducing the need for diagnostic thyroid lobectomy for indeterminate lesions has been studied to be negative predictive values 95 to 100%. While such preliminary studies are promising, further research is needed before observation could universally be recommended over surgery for non-18FDG-avid thyroid nodules with indeterminate FNA cytology(1). Even though 18 FDG-PET/CT does not play a role in the workup of a nodule,any 18 FDG - avid thyroid nodule found incidentally deserves a thorough workup for malignancy.

Fine needle aspiration cytology and the Bethesda system:

The procedure of FNAC and cytology examination was first developed by Ellis and Martin in the year 1930. At present, FNA cytology or thyroid gland biopsy has been accepted everywhere as the step with most importance in the pre operative evaluation any lesion in the thyroid gland. About 2,50,000 to 3,00,000 fine needle biopsies have been estimated to have been done over a period of one year in the United States. As the fine needle aspiration gives

the most accurate information regarding the composition of cells in any thyroid lesion, it has always been seen as the gold standard in diagnosis that will change subsequent decisions regarding management.

The guidelines for practise formulated by the American Thyroid Association have recommended that fine needle aspiration must be one of the early diagnostic investigations because it is highly reliable for diagnosis and is cost effective(11). Fine needle aspiration cytology plays an important part in the assessment of a bio chemically eu thyroid nodule. It decreases the need for surgery in patients that are diagnosed to have benign nodules.

It also categorises patients that are diagnosed to have thyroid cancer to the needful operation. Prior to routine cytology, the percentage of operated thyroid swellings that turned out to be malignant was 14%. With the present fine needle aspiration cytology practise, the percentage of surgically excised lesion that turn out to be cancers surpasses 50%(12).

Unfortunately, FNAC of any thyroid nodule is far from being perfect. It can provide results that are useful for diagnosis in only around 80% cases. The sensitivity and specificity are about 83% and 92%, respectively(11).

Before a FNAC is done, the gland must be thoroughly felt, the nodule that is for aspiration must be identified. This procedure must be told to the patient in a satisfactory manner and the patient's queries must be addressed. The patient is made to lie down flat on the examination table and extending his/her neck completely and a support is placed below the shoulders. Good lighting must be present.

The skin surface is cleaned with spirit. Then the patient is told to lie still during the placement of the needle. Anaesthesia is usually not needed. Usually a 27 gauge or 25 gauge 1.5 inch needle fixed with a 10mL disposable syringe is required. Some may use a mechanical holder for the syringe.

The needle is then plunged into the lesion without the use of suction and making sure that the tip of the needle is within the lesion. Suction is then applied while the needle is moved out and into the nodule. This motion helps to separate cellular material which will be sucked in to the needle. In a few seconds, the aspirate is seen within the hub of the needle.

When this happens. the suction is stopped, the needle can be taken out and smears can be made. Syringe is then separated from needle and air is sucked in by withdrawing the plunger. The syringe is re attached to the needle and a drop of the material that is aspirated is then put onto glass slides.

The smears are made using two glass slides, in a similar method to making blood smears. The slides thus prepared can be dried by air or fixed by submersing them in 95% alcohol for Papnicolaou stain. In some centers, automated cytology machinery like Thin Prep are used where the specimens are kept in a solution and seen later at the lab. Two or four passes are made from various sites in the nodule. In each aspiration, two or four slides can be prepared.

Non- aspiration biopsy of the nodule may be done. For this technique, a twenty five gauge needle is held as one would hole a pencil, at the hub , and is then inserted in the lesion to be aspirated. After the aspirate has flown into the hub, it is withdrawn.

The material that is collected into the shaft is put on slides. The smear is the prepared as previously described .

As soon as the needle is withdrawn, there must be immediate and gentle compression at the site of aspiration. This is to prevent formation of a hematoma. If the patient is comfortable and there are no problems, the patient can be allowed to leave.

The concern with Fine needle aspiration or biopsy is the number of falsely negative results, that may result in inadequate surgery and further create complications in management. The falsely negative results have been described as benign cytology in the FNA but provide a histological surprise by being diagnosed as carcinomas after surgery. The rates of these falsely negative results vary between 1.5% and 11.5% in various study series(11).

The reasons for these falsely negative results are mostly not clear. Some of the solutions include the use of ultrasound in guiding proper FNAC placement and aspiration of different nodules have been proposed to lower false negative reports. Sampling that is not adequate is one of the most crucial issues that changes the accuracy of the cytology other than human errors. Then, the error in the method of sampling usually occur when there are many nodules and when benign lesions are biopsied instead of the malignant ones(11).

Fine-needle capillary sampling — Fine-needle capillary sampling (FNC, also called fine-needle nonaspiration biopsy) is a variation of FNA in which the sample is obtained by repetitively moving within the nodule a 25- to 27-gauge needle that is not attached to a syringe. After the needle is removed from the nodule, a syringe containing air is used to express the sample on a slide, which is smeared, stained, and submitted for cytologic interpretation. An FNA done with the syringe attached to the needle but with no negative aspiration pressure provides similar results.(13)

FNA versus FNC — The negative aspiration pressure used for FNA may result in more tissue damage and bleeding than FNC. This is a potential problem since blood and fibrin can obscure cells and therefore limit the ability to interpret the specimen. The relative efficacy of these procedures was evaluated in a study of 104 thyroid aspirates.

The specimens obtained by FNA were significantly more likely to be non diagnostic than those obtained by FNC (16 versus 6 percent). In a second report, the percentage of non diagnostic samples at a variety of body sites was the same with both techniques, but the cytologic smears obtained with FNC were of higher quality.(13)

Complications — Local pain and hematomas are the most common complications, while serious adverse events are rare. This was illustrated in a systematic review of 13 studies including 18,156 individuals undergoing thyroid biopsy. The following findings were noted:

- Local pain and/or discomfort were minor, transient, and well-tolerated, but several studies reported subsets of patients (2 to 8 percent) with moderate pain lasting up to several days. Pain was more common when deep-seated, non palpable nodules were biopsied, but the procedure rarely had to be discontinued because of patient discomfort. Local lidocaine anaesthesia can help minimize pain.

- There was inconsistency in the reported frequency of hemorrhage/hematomas during or after thyroid biopsy with a range of 0.3 to 26 percent. Small to moderate-sized hematomas were managed with cold compresses and almost always resolved spontaneously within several days. Massive hematoma with airway obstruction was seen in only a few cases.

Other complications are rare and include acute transient thyroid swelling, infection, tracheal puncture, needle track seeding (ie, tumor implantation), and recurrent laryngeal nerve palsy with vocal cord paralysis. In another series, recurrent laryngeal nerve injury occurred in 4 out of 10,974 biopsies (0.036 percent), which resolved in all cases within six months.(13)

It is very important that cyto pathologists are able to communicate thyroid FNA reports to referring doctors using terms that are unambiguous and are helpful in making management decisions.

Historically, the terminology that have been used for thyroid FNA has always been a problem. It differed between laboratories leading to utter confusion and preventing sharing of data among various institutions.

Prior to the standardization of FNACs with the Bethesda system, the categories that were adopted were non diagnostic, benign, follicular / Hurthle neoplasm, suspicious for malignancy, and malignant.

In order to address these terminology related issues of thyroid FNA, the Bethesda System for Reporting Thyroid Cytopathology was made in 2007. To have clear communication, the Bethesda System suggests that every report begins with a "general diagnostic category". There are six general diagnostic categories. Some categories have 2 alternative names. Each one of these categories carries an implied risk of cancer which ranges between 0% to 3% for the benign group to almost 100% in the malignant group. This entire process connects to a management guideline that is rational and appropriate.

The six categories are as given below.

Table 1

The Bethesda System for Reporting Thyroid Cytopathology: Recommended Diagnostic Categories*

I.	**Nondiagnostic or Unsatisfactory**
	Cyst fluid only
	Virtually acellular specimen
	Other (obscuring blood, clotting artifact, etc)
II.	**Benign**
	Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc)
	Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context
	Consistent with granulomatous (subacute) thyroiditis
	Other
III.	**Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance**
IV.	**Follicular Neoplasm or Suspicious for a Follicular Neoplasm**
	Specify if Hürthle cell (oncocytic) type
V.	**Suspicious for Malignancy**
	Suspicious for papillary carcinoma
	Suspicious for medullary carcinoma
	Suspicious for metastatic carcinoma
	Suspicious for lymphoma
	Other
VI.	**Malignant**
	Papillary thyroid carcinoma
	Poorly differentiated carcinoma
	Medullary thyroid carcinoma
	Undifferentiated (anaplastic) carcinoma
	Squamous cell carcinoma
	Carcinoma with mixed features (specify)
	Metastatic carcinoma
	Non-Hodgkin lymphoma
	Other

* Adapted with permission from Ali and Cibas.[3]

(12)

Table 2

The Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Recommended Clinical Management

Diagnostic Category	Risk of Malignancy (%)	Usual Management†
Nondiagnostic or Unsatisfactory	1-4	Repeat FNA with ultrasound guidance
Benign	0-3	Clinical follow-up
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	~5-15‡	Repeat FNA
Follicular Neoplasm or Suspicious for a Follicular Neoplasm	15-30	Surgical lobectomy
Suspicious for Malignancy	60-75	Near-total thyroidectomy or surgical lobectomy§
Malignant	97-99	Near-total thyroidectomy§

FNA, fine-needle aspiration.

* Adapted with permission from Ali and Cibas.[3]

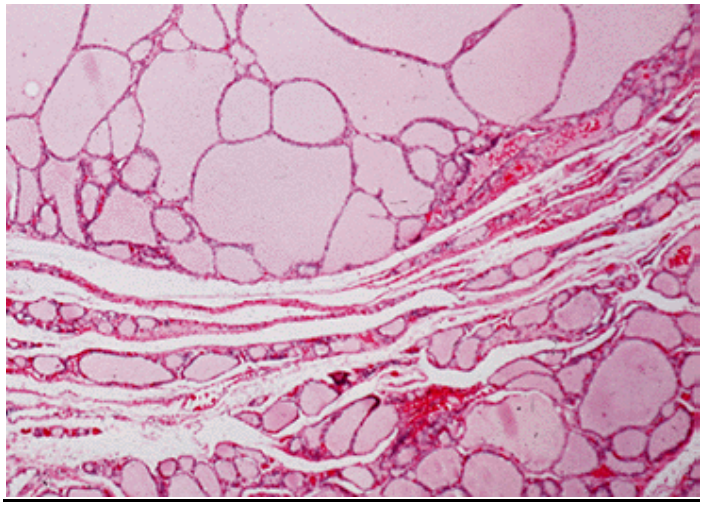
† Actual management may depend on other factors (eg, clinical, sonographic) besides the FNA interpretation.

‡ Estimate extrapolated from histopathologic data from patients with "repeated atypicals."

§ In the case of "Suspicious for metastatic tumor" or a "Malignant" interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated.

(14)

Non diagnostic or Unsatisfactory:



Colloid nodules that display macro follicles that are bordered by epithelial cells of thyroid origin. These nodules are well circumscribed and does not possess a fibrous capsule(15).

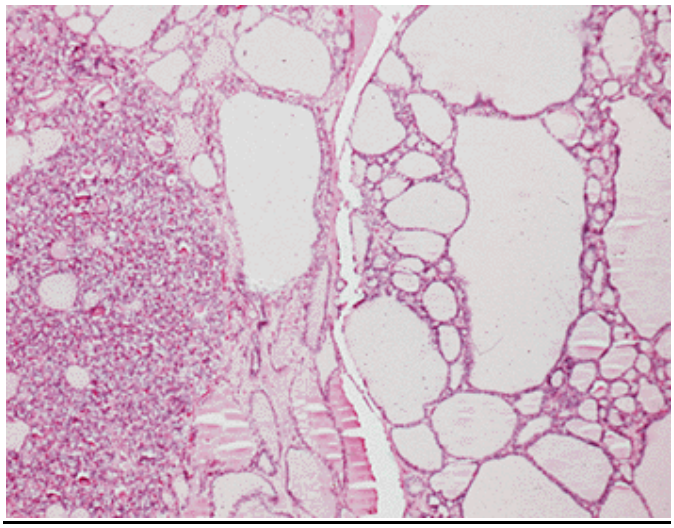
The adequacy of cells in every FNAC done, should be properly evaluated. Specimens that are inadequate are reported as “non diagnostic” (ND) or “unsatisfactory” (UNS). This also applies for groups of samples that are deemed not satisfactory because of excessive blood and improperly made smears and an inadequate number of follicular cells. If a thyroid FNAC specimen has to be satisfactory for evaluation, the minimum requirement is atleast 6 groups of benign follicular cells, each group comprising of at least 10 cells.

As usual, there are exceptions. Any sample which has lots of colloid is said to be adequate, even though six collections of follicular cells are absent. Any specimen that has a sparse number of cells with a lot of colloid is usually a predominantly macro follicular nodule and is almost always benign. When a particular diagnosis can be given and when there are any atypical cells, the sample is by implication, appropriate for further evaluation.

Non diagnostic or unsatisfactory results are seen in 2% to 20% of the patients, but ideally it should not exceed 10% of the FNACs, leaving out samples that are made almost entirely of macrophages.

A repeated aspiration with the guidance of ultra sound is recommended for this category and those FNACs that are clinically or sonographically worrying and is diagnostic in about 50% to 88% of cases. Surgical removal of the thyroid gland is one of the options for nodules that have been non diagnostic or unsatisfactory as ten percent are found to be malignant(12).

Benign:

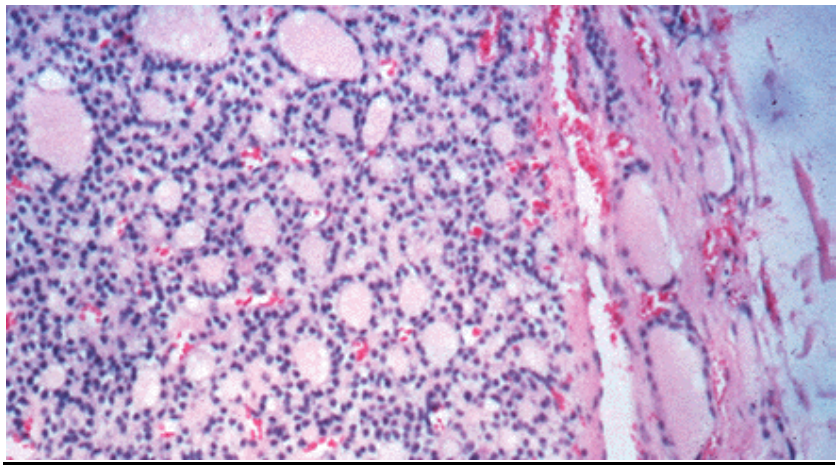


An area with nodular hyperplasia and a colloid nodule with macro follicles and focal hyperplasia that is suggestive of a benign nodule.(15)

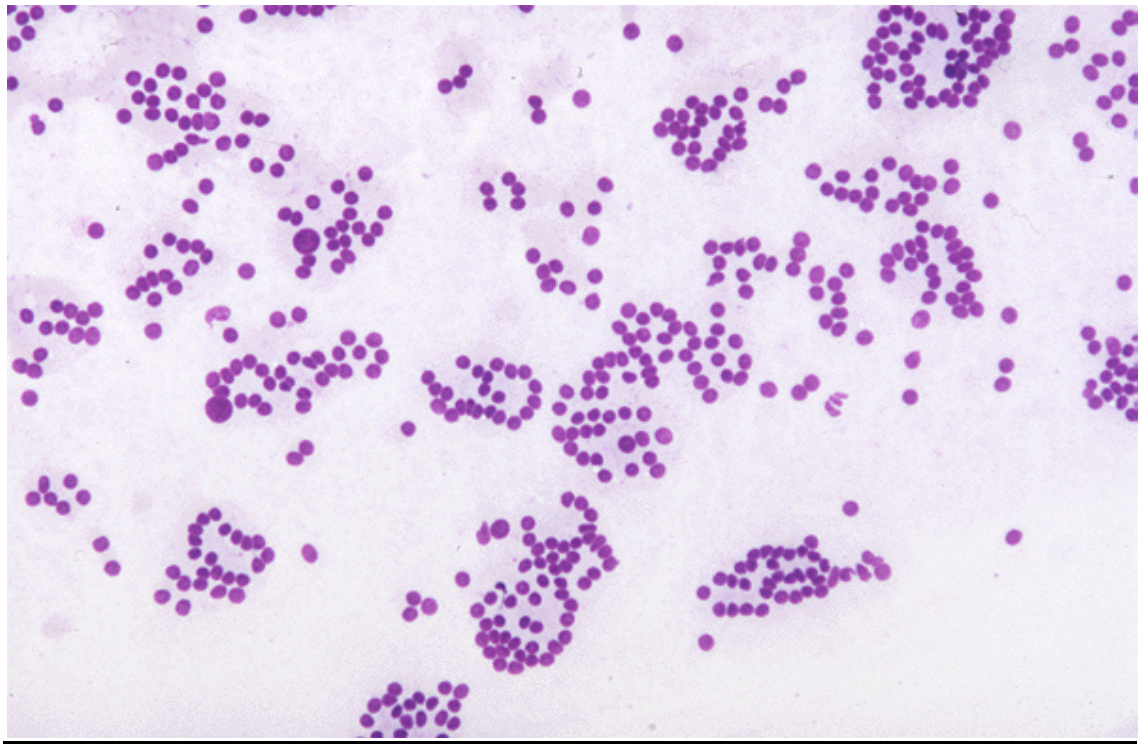
The benefit of a thyroid FNAC enables the surgeon to make a diagnosis of a benign lesion as correctly as possible thus avoiding the need of an unwanted surgery. A "benign" diagnosis is seen in about 60% or 70% of FNACs from the thyroid gland.

A benign interpretation carries a low risk of being falsely negative (0% to 3%), but these individuals are nevertheless re assessed by ultrasound and palpation every six to eighteen months. When the nodule that is being followed up shows rapid growth or any "suspicious" change on ultra sonography, then a repeat FNA must be considered(12).

Atypia of Undetermined Significance / Follicular Lesion of Undetermined Significance:



Nodule that shows micro follicles and is surrounded by an even fibrous capsule. There is no capsular or vascular invasion.(15).

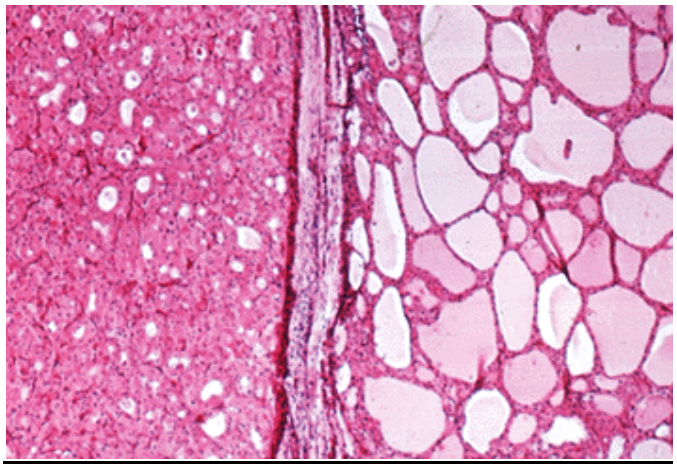


Some epithelial cells found in follicular arrangement that suggests an adenoma, which can be from a follicular carcinoma.(15)

Some cytologies may not be classified with ease into the categories of benign or suspicious or malignant. These are the cases that have been found to represent a small group of cytologies and are reported as atypia of undetermined significance (AUS) or follicular lesion of undetermined significance in the Bethesda System.

The risk for malignancy for an nodule that has been labelled as AUS is very tough to establish as only a small proportion of patients in this group have had surgery and follow up. The patients who have had an operation form a very focussed group of patients who have had FNACs with repeated AUS reports or in those patients who have clinical or sonological lesions that are worrisome. In this group, about 20% to 25% patients having atypia of undetermined significance prove to be of malignant nature after surgery(12).

Follicular Neoplasm / Suspicious for a Follicular Neoplasm:

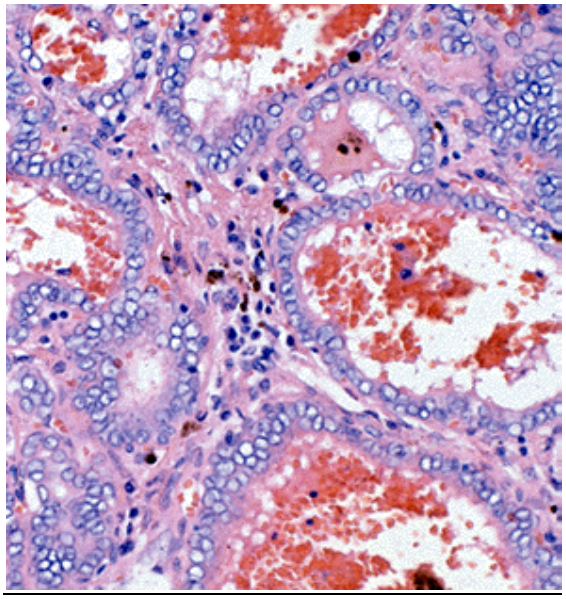


A Hurthle cell tumor, seen in the lower half of photograph showing well circumscribed margins established by an intact fibrous capsule. This is a Hurthle cell tumour of low malignant potential(15).

The intention of this group is to find those nodules that maybe follicular cancers and guide towards an operation. FNAC can be used to diagnose many thyroid diseases (eg: papillary cancer or lymphocytic thyroiditis), however, in regards to follicular carcinoma, it is often used as a tool for screening.

The majority of Follicular neoplasms/suspicious of follicular neoplasm cases turn out as Follicular adenomas or as adenomatoid nodules of a multi nodular goitre, which are more common than follicular cancer. Of those that are proven to be malignant, many are Follicular carcinomas. However a significant proportion of these are follicular variants of papillary carcinomas(12).

Suspicious for Malignancy:

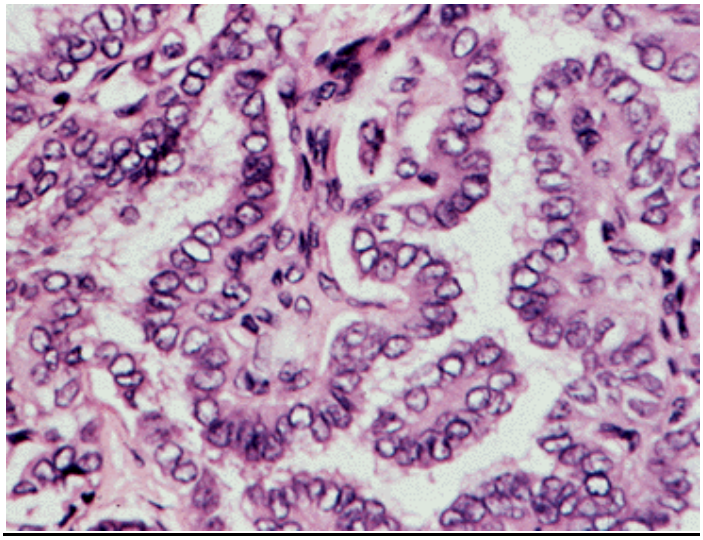


This is a follicular variant of papillary carcinoma with the typical vesicular nuclei and haemorrhage in the follicular lumens(15).

Many of these cancers, especially papillary cancer of the thyroid gland, may be precisely diagnosed with almost 100 % accuracy by FNAC. However , the nuclear, architectural metamorphosis of a few papillary cancers are focal and difficult to pick up. As is most commonly seen in the follicular variant of papillary cancers, which may be difficult to differentiate from a benign follicular nodule.

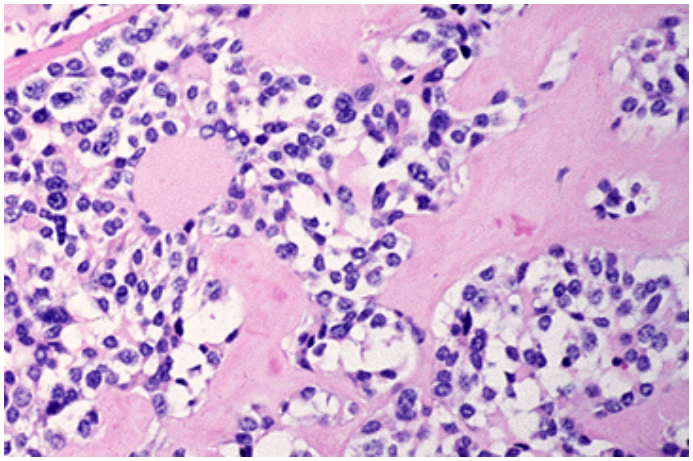
Nodules that are labelled as suspicious for papillary carcinoma of the thyroid gland are removed either through a lobectomy or a total thyroidectomy. Many of these (60%-75%) prove to be papillary carcinomas and the rest are usually follicular adenomas(12).

Malignant:

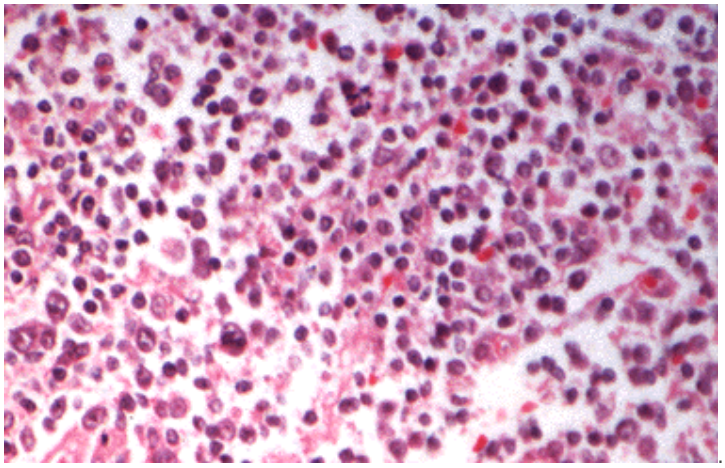


Papillary carcinoma thyroid. The structure is made of complex fibro vascular core of structures that are covered by crowded, overlapping, vesicular nuclei which are artifacts of fixation. Little colloid is seen. Such histologic foci may be encapsulated or sclerosing, invasive, or multi centric.(15)

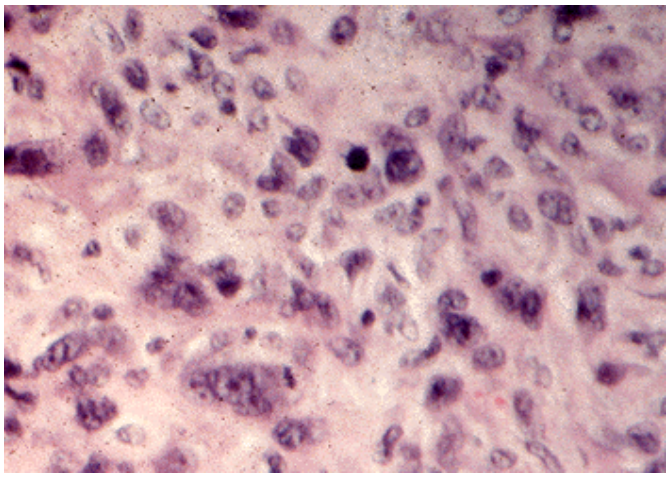
This group malignant is usually used when the cytology and morphology are diagnostic of malignancy. The description that is given below are those that are used to sub categorise the cancer and help to conglomerate the results in any special studies. About 3% to 7% of FNACs have these confirmative features of cancer and these are mostly are papillary cancers(12).



Medullary carcinoma thyroid with amyloid stroma(15)



Large cell lymphoma thyroid(15)



Anaplastic carcinoma of thyroid with pleomorphic giant tumour cell nuclei(15).

Recent studies:

There are no doubts about the clinical features that suggest an increased risk of malignancy in any thyroid nodule. They have been described time and time again in various surgical text books and further discussion will not be necessary. However, the move to introduce the Bethesda system of reporting for FNACs of thyroid nodules has been fairly recent. After the introduction of the Bethesda system, there have been few studies for validation and literature as regards experience with the system in various centers. Atypia of undetermined significance group has been of particular interest.

In a study conducted at Christian Medical College, Vellore (not yet published), out of 1018 patients operated for thyroid nodules during the study period, 404 (39.7%) were follicular lesions. Mean (±SEM, range) age of patients was 41 years (± 0.78, 12 -78) and M:F were 1:4.

FNAC showed suspicious for malignancy in 30% (n=43) patients based on higher cellularity, nuclear atypia and thick scanty colloid (p0.001). FNAC was suggestive of benign in 100

patients but finally turned out malignant on histopathology. Lesions with nodule size > 3cm had 51% malignancy rate (p0.004). The most common histological variants were papillary thyroid cancer (39.2%) including classical (20%), follicular (18%) and micro carcinoma (1.2%) variants followed by nodular hyperplasia (19.3%), follicular adenoma (4%) and follicular carcinoma (3%). Completion surgery was needed in 47 patients.

The conclusion from the above study was that nodular hyperplasia & papillary thyroid cancer were most common histological variants in follicular lesions. This supports surgical resection for "suspicious for malignancy" & "follicular neoplasm", selective use of surgical intervention for "follicular lesions - probably benign" and continued efforts to define unified terminology.

In 2009, Nayar R and Ivanovic M from the Department of Pathology, Northwestern University, Feinberg School Of Medicine, Chicago, Illinois published a retrospective study on 5194 thyroid nodules. Their conclusion were:

The Indeterminate category comprised of 18% of all FNACs. Cytology was followed up in 21 percent of indeterminate patients in which 58 percent was benign / negative and did not go on to surgery based on the cytology alone.

Surgical follow up in 46 percent of indeterminate cases showed 52 percent were benign / negative and 42 percent were follicular or Hurthle cell adenomas. The surgical report of malignancy in such cases was low (6%) when seen against the Follicular neoplasm group, which was 14 percent , more than two times the indeterminate category and the suspicious of malignancy group which was 53 percent (almost nine times that of the indeterminate category).

The conclusion that they reached was that a 6-tier reporting system for thyroid FNA was effective for determining which patients needed surgery versus follow-up FNA and also guided the clinician on the extent of surgery(16).

Another study was published in May 2012 by Wu HH, Rose C, Elsheikh TM from Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, Indiana. They applied the Bethesda terminology in 1,382 thyroid cytologies in a community setting, which included 539 cases of Benign (39 percent), 376 cases of atypia of undetermined significance (27.2 percent), 116 cases of follicular neoplasm (8.4 percent), 37 cases of malignant (2.7 percent), 36 cases of suspicious of malignancy (2.6 percent), and 278 cases of inadequate FNAs (20.1 percent).

221 cases (16 percent) of thyroid cytologies had follow up thyroid surgeries. On follow up based on histology, the chance of malignancy was benign 3%, atypia of undetermined significance 6%, follicular neoplasm 22%, suspicious of malignancy 56%, and malignancy 100%.

The conclusion that they reached were that classification and recommendation for follow up in the Bethesda classification are accurate for every category. Both benign as well as atypia of undetermined significance are lesions of low risk and carry a low probability for malignancy. Follicular neoplasms indicate a greater rate for malignancy but an intermediate

risk for malignancy while those lesions that are suspicious of malignancy carry a high risk for malignancy(14).

Most the studies that have been published in relation to the Bethesda system have been single center, retrospective studies without ultra sound and clinical correlation. Further more, there are no data available on the Indian population.

In another study from the Department of Head and Neck Surgery at the Memorial Sloan Kettering Cancer Centre, New York and Cleveland Clinic, Cleveland that was published in 2010 a nomogram to that will predict the likelihood of malignancy in the evaluation of any thyroid nodule was proposed.(17)

Patients presenting with thyroid nodules who under went ultrasonography and guided aspiration with thyroidectomy at the institutions during the period between 2007 and 2008 were recruited. The records along with their bio chemical reports, pathology results, ultrasonography images with cytology was reviewed. The malignancy risk was then calculated using a multi variate logistic regression(17).

The charts of 158 cases that had 190 lesions were then reviewed(17). Eighteen cases were then excluded for various reasons.

The eight variables that had the highest predictive value that were then put into the nomogram were TSH, ultra sound (echo texture, shape and vascularity) with cytology (pseudo inclusions, nuclear grooving, cellularity in the background of colloid)(17). This nomogram was found to have a very good predictive accuracy and a good concordance index of 91 percent(17).

Table III. Variables with the greatest predictive value for diagnosing malignancy

Predictor variable	*Variable category*	*Odds ratio*	*95% CI*	P *value*
TSH*	2.24 (Q3) vs 1.19 (Q1)	3.53	1.35–9.24	.0305
Shape	Taller than wide vs oval	3.20	0.24–43.50	.1840
	Variable vs oval	0.78	0.16–3.79	.3822
Echo texture	Mixed vs hypoechoic	1.28	0.27–6.00	.7531
	Isoechoic vs hypoechoic	0.34	0.1–1.16	.0848
Vascularity	Hypervascular vs none	0.06	0.004–0.75	.0292
	Hypovascular vs none	0.04	0.003–0.49	.0124
	Mixed vs none	0.02	0.002–0.31	.0042
	Perinodular vs none	0.06	0.004–0.91	.0426
Nuclear grooves	Present vs absent	35.81	9.24–138.79	<.0001
Nuclear pseudoinclusions	Present vs absent	7.32	1.37–39.11	.0198
Aspirate cellularity	Hypercellular vs moderately	2.01	0.59–6.92	.0570
	Hypocellular vs moderately	0.22	0.05–1.05	.0570
Colloid	Abundant vs scant	0.26	0.07–0.95	.0421

*An increase in TSH from quartile 1 (1.19) to quartile 3 (2.24) with all other predictors constant increases the odds of malignancy within the nodule by a factor of 3.53.

(17)

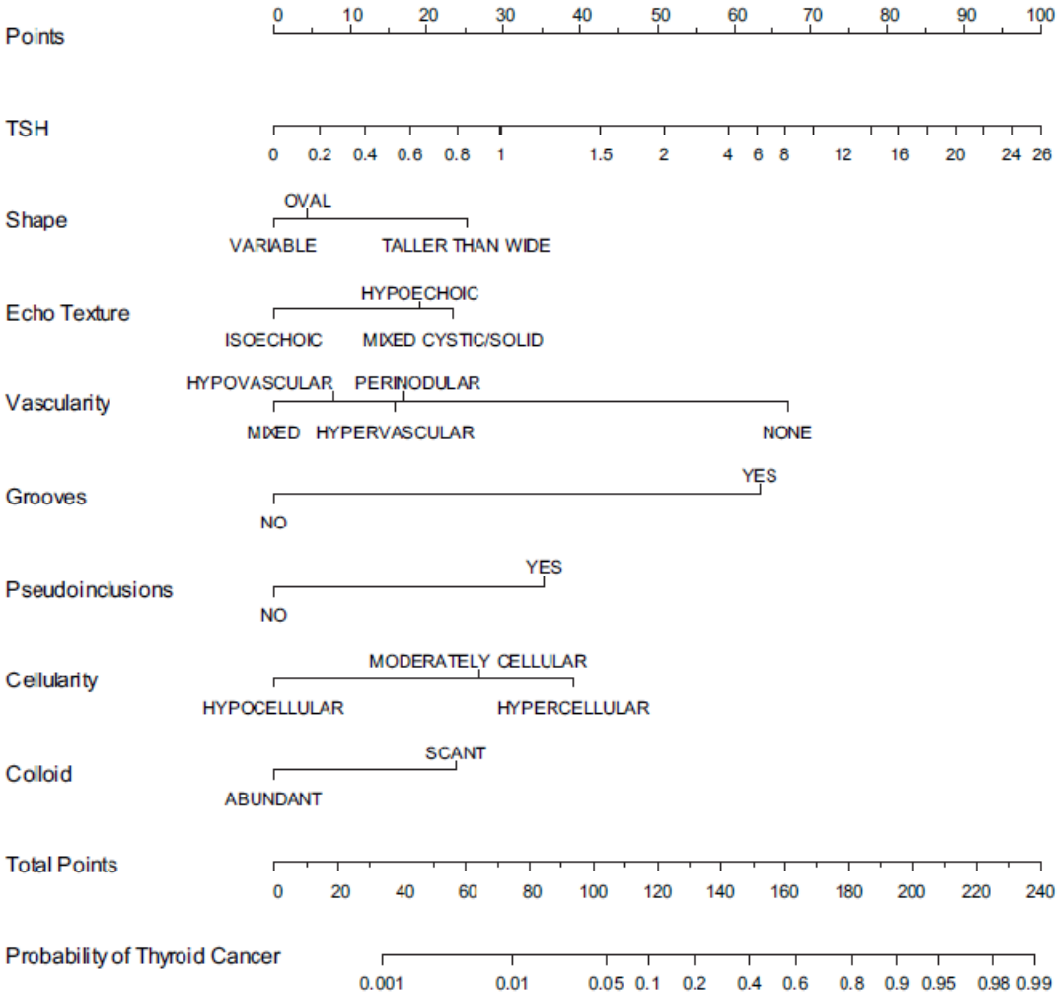


Fig 1. Nomogram (concordance index = 0.911).

(17)

Summary:

The evaluation of a thyroid nodule often posts a challenge to the treating surgeon. If allowed to borrow a term from the evaluation of breast cancers, triple assessment would be the right terminology to use to describe thyroid nodule assessment. A clear understanding of the clinical features, ultrasound findings and the implications of a FNA report is essential to the management of the thyroid nodule.

METHODS:

All patients presenting with newly diagnosed nodule of thyroid were included in this study. Patients having external cytology / ultrasound were reassessed if agreeable to participate. Slide reviews were accepted if smears were considered adequate by the pathologists. All ultrasounds were repeated as the information that was required for this study maybe be inadequately reported from ultra sounds elsewhere. Ultra sound guided FNACs were done if the clinicians felt it was required.

Performa was filled either in the out patient department or after admission to the ward. The clinical assessment was done by a senior consultant. Most ultra sonograms were done by the designated radiologist, before the FNACs were done.

Cytology was reported as per the Bethesda criteria. The gold standard for diagnosis in this study was taken as the histopathology result.

The study was conducted in the time period between May 2011 and June 2012. There were 102 cases with malignant histopathology versus 93 cases of benign histopathology.

The following clinical criteria were used to indicate increased risk of malignancy:

- Age >40 YRS
- Male gender
- Family history of thyroid malignancy
- Persistent dysphonia, dysphagia or cough
- Consistency - hard
- Fixed swelling

FNAC CRITERIA:

- I. Non diagnostic or Unsatisfactory
- II. Benign
- III. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance
- IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm
- V. Suspicious for Malignancy
- VI. Malignant

ULTRA SOUND CRITERIA:

- Punctate micro calcifications
- Hypoechogenicity
- Irregular margins or no halo
- Solid/cystic/mixed
- Intra nodule vascularity
- More tall than wide
- Lymph nodes - cystic

The information was entered into Epi Data and analysed using SPSS after conversion to an excel spreadsheet.

RESULTS:

Table 1 : Age distribution of cases

			Cases		
			malignant	benign	Total
age	15 - 40	No.	64	35	99
		% within age	64.6%	35.4%	100.0%
	41-50	No.	22	33	55
		% within age	40.0%	60.0%	100.0%
	>51	No.	16	25	41
		% within age	39.0%	61.0%	100.0%
Total		No.	102	93	195
		% within age	52.3%	47.7%	100.0%

P value = 0.002

TAble 2: Sex distribution

			Cases		
			malignant	benign	Total
Sex	female	No.	69	64	133
		%	51.9%	48.1%	100.0%
	male	No.	33	29	62
		%	53.2%	46.8%	100.0%
Total		No.	102	93	195
		%	52.3%	47.7%	100.0%

P=0.861

Table 3 : Features of compression or nerve involvement

		Cases		
		malignant	benign	Total
	Asymptomatic	85	76	161
	%	52.8%	47.2%	100.0%
	Symptomatic	17	17	34
	%	50.0%	50.0%	100.0%
Total	Count	102	93	195
	%	52.3%	47.7%	100.0%

P=0.767

Table 4: Dominant consistency

Dominant consistency		cases		
		malignant	benign	Total
	Hard	11	1	12
	%	91.7%	8.3%	100.0%
	Soft	2	1	3
	%	66.7%	33.3%	100.0%
	Cystic	0	3	3
	%	.0%	100.0%	100.0%
	Firm	89	88	177
	%	50.3%	49.7%	100.0%
Total		102	93	195
	%	52.3%	47.7%	100.0%

P=0.01

Table 5: Fixity to surrounding structures

		cases		
		malignant	benign	Total
fixity	No	98	93	191
	%	51.3%	48.7%	100.0%
	Yes	4	0	4
	%	100.0%	.0%	100.0%
Total	Count	102	93	195
	%	52.3%	47.7%	100.0%

P=0.054

Table 6: FNAC

FNAC	Benign	Malignant	Total
Non diagnostic or un-satisfactory	26 (54.1%)	23 (47.9%)	48
Benign	41 (66.1%)	21 (33.9%)	62
AUS	15 (44.1%)	19 (55.9%)	34
Follicular neoplasm	9 (39.1%)	14 (60.9%)	23
Suspicious for malignancy	1 (8.3%)	11 (91.7%)	12
Malignant	0	15 (100%)	15

P=0.00

Table 7: Punctate micro calcification on ultra sound

Punctate micro calcification		cases		
		malignant	benign	Total
	No	55	85	140
	%	39.3%	60.7%	100.0%
	Yes	47	8	55
	%	85.5%	14.5%	100.0%
Total		102	93	195
	%	52.3%	47.7%	100.0%

P=0.000

Table 8: Hypoechogenicity

Hypo echogenicity		Cases		Total
		malignant	benign	
	No	55	62	117
	%	47.0%	53.0%	100.0%
	Yes	47	31	78
	%	60.3%	39.7%	100.0%
Total		102	93	195
	%	52.3%	47.7%	100.0%

P=0.07

Table 9: Irregular margins

Irregular margins		cases		
		malignant	benign	Total
	No	89	87	176
	%	50.6%	49.4%	100.0%
	Yes	13	6	19
	%	68.4%	31.6%	100.0%
Total		102	93	195
	%	52.3%	47.7%	100.0%

P=0.139

Table 10: Dominant consistency

Consistency		Malignant	Benign	Total	P value
Solid	Yes	47(71.2%)	19(28.8%)	66	0.00
	No	55(42.6%)	74(57.4%)	129	
Cystic	Yes	3(23.1%)	10(76.9%)	13	0.029
	No	99(54.4%)	83(45.6%)	182	
Mixed	Yes	55(45.8%)	65(54.2%)	120	0.022
	No	47(62.7%)	28(37.3%)	75	

Table12: Intra nodule vascularity

Intra nodule vascularity		Cases		
		malignant	benign	Total
	No	44	56	100
	%	44.0%	56.0%	100.0%
	Yes	58	37	95
	%	61.1%	38.9%	100.0%
Total		102	93	195
	%	52.3%	47.7%	100.0%

P=0.017

Table 13: More tall than wide

More tall than wide		cases		
		malignant	benign	Total
	No	87	75	162
	%	53.7%	46.3%	100.0%
	Yes	15	18	33
	%	45.5%	54.5%	100.0%
Total	No.	102	93	195
	%	52.3%	47.7%	100.0%

P=0.387

Table 14: Significant lymph nodes.

Significant lymph nodes		Cases		
		malignant	benign	Total
	No	75	88	163
	%	46.0%	54.0%	100.0%
	Yes	27	5	32
	%	84.4%	15.6%	100.0%
Total	No.	102	93	195
	%	52.3%	47.7%	100.0%

P=0.000

Table 15: Clinical size

Size in cms			Cases		
			malignant	benign	Total
size	0-3		46	33	79
		%	58.2%	41.8%	100.0%
	3-6		41	37	78
		%	52.6%	47.4%	100.0%
	>6	Count	15	23	38
		%	39.5%	60.5%	100.0%
Total		Count	102	93	195
		%	52.3%	47.7%	100.0%

P=0.164

Table 16: Size by ultra sound

Size in cms		cases		
		malignant	benign	Total
size	0-3	52	51	103
	%	50.5%	49.5%	100.0%
	3-6	43	29	72
	%	59.7%	40.3%	100.0%
	>6	7	13	20
	%	35.0%	65.0%	100.0%
Total		102	93	195
	%	52.3%	47.7%	100.0%

P=0.1275

DISCUSSION:

From Table 1, it is clear that most of our patients were in the age group 15 – 40 yrs. There were more number of benign thyroid swellings than malignant, which was statistically significant(P=0.002).

However, literature tells us that malignant swellings are common in the younger and older extremes of age(9). This is not reflected here in this study. It could be because, there were lesser number of patients in the >50yrs age groups.

Table 2 shows us that there were more number of females enrolled into the study than males. But the number of benign and malignant thyroid swellings were almost equally distributed in the male group.

This is contrary to literature that tells us that being of male sex is a risk factor for malignancy(9).

Table 3 tells us that even though traditionally features of compression or nerve involvement have been considered as features of malignancy, it may not be the case.

Table 4,5 and 6 shows us that hard consistency, fixity are definite risk factors for malignancy with a significant P values.

Table 7 tells us how the Bethesda criteria works with the Indian population. There were a large number of non diagnostic or unsatisfactory FNACs. The percentage of malignancy was 47.9% .

Literature describes the risk of malignancy in the non diagnostic or unsatisfactory FNACs to be 1 - 4%(12). The high number of ND/US FNACs may be because most of these FNAs are not done ultra sound guided and done by relatively inexperienced residents, at an early stage of their surgical training.

There were also a large number of cases reported as benign in the FNAC, in which the final histopathology report was malignant(33.9%). The risk as reported by the Bethesda criteria was 0-3%(12).

The atypia of undetermined significance(AUS) group has always been of interest to researchers all over the world. There were 34 cases in this group of which, 19 were malignant ie; 55.9%.

The suspicious of malignancy and malignancy group percentages were in keeping with the Bethesda criteria(12).

From tables 8, 9, 10, 11, 12, 13, 14, we can infer that the punctuate micro calcifications, hypo echogenicity, intra nodule vascularity and significant lymph nodes are risk factors to indicate malignancy. A solid consistency of the nodule is a risk factor for malignancy while a cystic nature indicates that it is more likely benign.

Tables 15, 16 tell us that size may not be a significant risk factor for malignancy inspite of iterature telling us otherwise.(2)

CONCLUSIONS:

1) Older age and male gender were not risk factors for malignancy.

2) Features of compression was not a risk factor for malignancy.

3) Hard consistency, fixity were definite risk factors for malignancy.

4) The Bethesda system will need further validation among the Indian population.

5) FNACs have better yield and clinical value when done ultra sound guided than manually.

6) Ultra sound features that are significant are punctuate micro calcifications, hypo echogenicity, intra nodule vascularity, solid consistency and significant lymph nodes.

7) Size was not a risk factor for malignancy in this study

LIMITATIONS:

This study was conducted in a single centre. As evident above, the sonological features and clinical assessment of a thyroid nodule is very observer independent. An ideal study design would be to involve multiple centres and a wide demography of patients.

In spite of best efforts to make a single radiologists do all the ultra sonograms, we had to succumb to the impossible logistics of the above proposition. This being a teaching centre and because of the sheer load of ultra sonograms that are done in a single day by the Department of Radiology, we had to accept that different radiologists could do the ultra sonogram as long as they adhere to the Proforma that we had given them for the thyroid ultra sound.

Previous similar studies have had a large sample size. Most have been retrospective studies making it much easier to acquire a large sample size. However, this was a prospective study, over a period of one and a half years, making it difficult to attain a larger sample size. No doubt, a larger sample size would have increased the significance of the study.

CONSENT:

I understand that I am taking part in a research study on thyroid nodules. My participation in the study is until I get my final histopathology report after surgery. Taking part in this study does not involve any tests other than which I would normally undergo as a part of evaluation of my thyroid nodule. The risks and unforeseen complications of taking part in this study is the same as any other non study patient. I also understand that my records will be kept confidential and only the author of this study will have access to it. My participation is voluntary, and i can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefit.

All of the above has been explained to me in my own language.

আমি বুঝতে পারি যে আমি একটি থাইরয়েড nodules গবেষণা গবেষণায় অংশ নিচ্ছি. গবেষণায় আমার অংশগ্রহণ পর্যন্ত আমি অস্ত্রোপচারের পর আমার histopathology চূড়ান্ত প্রতিবেদন পেতে. এই গবেষণায় অংশ নেওয়ার কোনো পরীক্ষা ব্যতীত অন্য যা সাধারণত আমি আমার থাইরয়েড অর্বুদ মূল্যায়ন একটি অংশ হিসাবে সহ্য করা হবে সঙ্গে যুক্ত নয়. ঝুঁকি এই গবেষণায় অংশ গ্রহণ এবং অভাবিত জটিলতা থেকে নল অধ্যয়ন রোগী হিসাবে একই. আমি বুঝতে পারি যে আমার রেকর্ড রাখা গোপন করা হবে এবং শুধুমাত্র এই গবেষণার লেখক এটি অ্যাক্সেস থাকবে. আমার অংশগ্রহণ স্বেচ্ছাসেবী, এবং আমি কোন সময় এবং যে অস্বীকার কোন লাভ বা ক্ষতি শাস্তি না জড়িত করা হবে অংশগ্রহণ এ গবেষণা থেকে নিজেকে প্রত্যাহার করতে পারেন.

উপরোক্ত সমস্ত সম্পর্কে যাও করেনি আমার নিজের ভাষায় ব্যাখ্যা করা হয়েছে.

□□□ □□□□□ □□□ □□ □□□ □□□□□□□ □□□□ □□□ □□□□□□ □□□ □□□ □□ □□□ □□□. □□□□□□ □□□ □□□□ □□□□□□□□ □□ □□□ □□□□□□ □□ □□□ □□□□ □□□□□ □□□□□□□□□□□□□□□□□□ □□□□□□□ □□□□□ □□. □□□□□□ □□□ □□□ □□□□ □□□ □□□□ □□ □□□□□□□ □□ □□ □□□□ □□ □□□□□ □□□ □□□ □□□ □□□□ □□□□□□□ □□□□□□ □□ □□□□□□□□□ □□ □□□ □□ □□□ □□□ □□□□□□ □□□□ □□□□□ □□. □□□□□□ □□□ □□□ □□□□ □□ □□□□□ □□ □□□□□□□□□□□□ □□□□□□□□ □□□□ □□ □□□□ □□□ □□□□□□ □□□□ □□ □□□ □□□ □□ □□. □□□ □□ □□□□□ □□□ □□ □□□□ □□□□□□□ □□ □□□□□□ □□□ □□□□□ □□□□ □□□□□□ □□ □□□□□ □□□□ □□ □□□ □□□□□ □□□□. □□□□ □□□□□□□□ □□□□□□□□□□ □□, □□□ □□□□ □□ □□□□ □□ □□□ □□ □□□ □□ □□□□□□ □□ □□□□□ □□□□ □□□□ □□□□□ □□□ □□□□ □□ □□□□□ □□□□□□ □□ □□□□ □□ □□□□ □□□.

□□□□□□□ □□□ □□□□ □□□ □□ □□□□ □□□ □□□□ □□□ □□ □□□□ □□□□□□.

□□□□ □□□□□□□□ □□□□□□□□□□□ □□□ □□□□□□□□□ □□□□□ □□□□□□□□□□□□□□□□ □□□□□□ □□□□□□ □□□□□□□□□. □□□□ □□□□□ □□□□□□□□□□□□ □□□□□ □□□ □□□□□ □□□□□□□□□□□□□□□ □□□□□□□ □□□□□□□□□□ □□□ □□□□□□□ □□□ □□□□□ □□□□□□. □□□□ □□□□□□□ □□□□□□ □□□□□□□ □□□□ □□□□□□□□ □□□ □□□□□□□□ □□□□□□□□ □□□□□□□□□□□□□□□ □□□ □□□□□□□□ □□□□□□□□□□□□□□□ □□□□ □□□□ □□□ □□□□ □□□□□□□□□□ □□□□□□□□□ □□□□□. □□□□ □□□□□□□ □□□□□□ □□□□□□□ □□□□□□□□□□ □□□□□□□□ □□□□□□□□□□□ □□□□□□□□□□□ □□□□ □□□□□□ □□□□□□ □□□□□□□□ □□□□. □□□□ □□□ □□□□□□□□□ □□□□□□□□□ □□□□□□□□□□□□□ □□□□ □□□□□ □□□□□□ □□□□□□□□ □□□□□□□□□ □□□ □□□□ □□□□□□□□□ □□□□□□ □□□□□□□□□ □□□□□□□. □□□ □□□□□□ □□□□□□□□□ □□□□□□□ □□□□ □□□□ □□□□□□ □□□□□□□□ □□□□□□□□□□□ □□□□ □□□□□□□ □□□□□□□ □□□□□□□ □□□□□□□□□□□□□□□ □□□□□□□□□ □□□□□□□□□ □□□□□□ □□□□□□□□□ □□□□□□ □□□□□□□□ □□□□□□□□ □□□□□□□□□.

□□□□ □□□□□□□□ □□□ □□□□□□□ □□□□□□□□□□ □□□□□□□ □□□□□□□□□□.

Patient's Sign: Doctor's sign:

PATIENT INFORMATION SHEET:

This sheet is to give you a basic idea of the study that you are part off. This study is on thyroid nodules. At present, there is no way to predict the likelihood of cancer in your thyroid swelling. The aim of this study is to form a scoring system to predict cancer. All the information will be collected in the form of clinical examination, ultra sound neck and FNAC neck. There is another proforma that we will be filling once the results of your test are out. These are the investigations that any patient with a thyroid nodule will undergo. You will not be subjected to any extra investigations or your treatment will not be compromised in any way. All the information collected for this study will be kept confidential and patient identity will not be revealed. However, for the sake of furtherment of science, the results may have to be published in international, national journals. If at any point you wish to withdraw from the study, you are free to do so. Contact information for any doubts that you may have are given below.

रोगी सूचना पत्रक:

इस पत्रक के लिए आप अध्ययन है कि आप हिस्सा बंद कर रहे हैं की एक बुनियादी विचार दे रहा है.इस अध्ययन थायरॉयड पिंड पर है. वर्तमान में, वहाँ कोई अपने थाइरोइड सूजन में कैंसर की संभावना का अनुमान है. इस अध्ययन का उद्देश्य के लिए एक स्कोरिंग प्रणाली के लिए कैंसर की भविष्यवाणी रूप है. सभी imformation नैदानिक परीक्षा, अल्ट्रा ध्वनि गर्दन और FNAC गर्दन के रूप में एकत्र किया जाएगा. इन जांच कि एक थायरॉयड ग्रंथि के साथ किसी भी मरीज से गुजरना होगा. आप किसी भी अतिरिक्त जांच के अधीन नहीं होगा. सभी इस अध्ययन के लिए एकत्रित की गई जानकारी को गोपनीय रखा जाए और रोगी की पहचान उजागर नहीं किया जाएगा. हालांकि, विज्ञान की furtherment की खातिर, परिणाम के लिए अंतर्राष्ट्रीय, राष्ट्रीय पत्रिकाओं में प्रकाशित किया जा सकता है. किसी भी बिंदु पर यदि आप अध्ययन से वापस चाहते हैं, तो आप ऐसा करने के लिए स्वतंत्र हैं.

□□□□ □□□□□□ □□□□□□□ □□□□ □□□□□ □□□□□ □□□□□ □□□ □□□□□□□□ □□□□□□ □□□□□. □□□□ □□□□□ □□□□□□□□ □□□□□□□□□□□ □□□□□□. □□□□□□□□, □□□□□□ □□□□□□□□ □□□□□□□ □□□□ □□□□□□□□□□□ □□□□□□□□□ □□□□□□ □□□□ □□□□□□□ □□□□□. □□□□ □□□□□□□ □□□□□□□□ □□□□□□□□□□□ □□□□□□□ □□□ □□□□□□□□□□□□□ □□□□□□□□ □□□□□□□□ □□□□□□□□. □□□□□□□ □□□□□ □□□□□□□□ □□□□□□□□□, □□□□□□□ □□□□□□□ □□□□□□□ □□□□□□□ FNAC □□□□□□□ □□□□□□□□□□ □□□□□□□□□□□□□□□□□. □□□□□□ □□□□□□ □□□□□□□□□ □□□□ □□□□ □□□□□□□□□ □□□□□ □□□□□□□□ □□□ □□□□□□. □□□□ □□□ □□□□□□□□ □□□□□□□□ □□□□ □□□□□□□ □□□□□ □□□□□ □□□□□□□ □□□□□□□□□. □□□□□□□ □□□□ □□□□□□□ □□□□□□□ □□□□□□□□□□□□□□□□□□ □□□□□□ □□□□□□ □□□□□□□□ □□□□ □□□□□□□ □□□□□□ □□□□□□□□. □□□□□□□ □□□□□ □□□□□□□ □□□□□□□ □□□□□□□□□□□□□□□□□□□□ □□□□□□ □□□□□□ □□□□□□□□ □□□□ □□□□□□□ □□□□□□ □□□□□□□□. □□□□□□□ □□□□□ □□□□□□□ □□□□□□□ □□□□□□□□□□□□□□□□□□□□ □□□□□□ □□□□□□ □□□□□□□□ □□□□ □□□□□□□ □□□□□□ □□□□□□□□.

□□□□ □□□□□□ □□□□□□□□□□□□□□□□□□□□ □□□□□□□ □□□□□ □□□□□□ □□□□□□□ □□□□□□□ □□□□□□ □□□□□ □□□□□□□□ □□□□□□□□□□□□□. □□□□□□□□□□□□, □□□□□□□□ furtherment □□□□□□□□□□, □□□□□□□□□□, □□□□□□□ □□□□□□□□□□□□□□□ □□□□□ □□□□□□□□□□□□□ □□□□□□□□□. □□□□□□□ □□□□□ □□□□□□□ □□□□□□□ □□□□□□□□□□□□□□□ □□□□□ □□□□□□□□□ □□□□□□□□□□, □□□□□□□ □□□□□ □□□□□□□. □□□□□□□□ □□□□□□□□□□□□ □□□□□□□□□□□□ □□□□□ □□□□□□□□□ □□□□□ □□□□□□□□□.

এই পত্রকে আপনি একটি গবেষণা উপজীব্য যে আপনি বন্ধ অংশ দিতে হয়. এই চর্চা থাইরয়েড nodules হয়. বর্তমানে, কোন উপায় আপনার ফুলে থাইরয়েড ক্যান্সার সম্ভাবনা ভবিষ্যদ্বাণী করা হয়. এই গবেষনার উদ্দেশ্য একটি স্কোরিং সিস্টেমের ক্যান্সার গঠন ভবিষ্যদ্বাণী করা হয়. সমস্ত তথ্য ক্লিনিকাল পরীক্ষা, অতি শব্দ ঘাড় এবং FNAC ঘাড় ফর্ম সংগ্রহ করা হবে. অন্য দর্শনার্থ পর্যন্ত যে আমরা ভর্তি একবার আপনার পরীক্ষার ফলাফল আউট করা হবে. এগুলি হল যে একটি তদন্ত থাইরয়েড অর্বুদ সঙ্গে কোনো রোগীর সহ্য করা হবে. আপনি অতিরিক্ত কোনো তদন্ত যাও চলছে করা হইনি বা আপনার চিকিৎসা কোনো ভাবে আপোস করা হবে না. সমস্ত তথ্য এই অধ্যয়নের জন্য সংগৃহীত রাখা গোপনীয় এবং রোগীর পরিচয় প্রকাশ করা হবে না হবে.

বিজ্ঞান furtherment অনুরোধে জন্য যাইহোক, ফলাফল আন্তর্জাতিক প্রকাশিত করা হবে জাতীয় পত্রিকা আছে, হতে পারে. যদি কোন বিন্দু আপনি গবেষণা থেকে নিজেকে প্রত্যাহার করতে চান, তাহলে হয় সেটা বিনামূল্যে. কোনো সন্দেহ জন্য যে তথ্য আপনি পারেন নিচে দেওয়া আছে সাথে যোগাযোগ করুন.

Contact information:

Dr. Vimalin Samuel

PG Registrar, Department of endocrine surgery, Cmc, Vellore, Mobile no: 9894180990

CHRISTIAN MEDICAL COLLEGE, VELLORE

TRIPLE ASSESSMENT OF SOLITARY NODULE OF THYROID

NAME: HOSPITAL NUMBER: or BRADMA:

DATE (OF FIRST ASSESSMENT):

CLINICAL ASSESSMENT:

- AGE: (1) 15-40yrs (2)40=50 yrs (0) >50yrs
- SIZE OF NODULE:
- SEX: (1) MALE (0)FEMALE
- FAMILY HISTORY OF THYROID MALIGNANCY (1) Y (0) N0
- PERSISTENT DYSPHONIA, DYSPHAGIA OR COUGH (1) Y (0) N
- DOMINANT CONSISTENCY – (1) HARD (2) CYSTIC (3) SOFT
- FIXED SWELLING (1) Y (0) N

  EXTRA THYROID EXTENSION (1) Y (0) N

FNAC: *(TO BE DONE FROM THE BODY OF THE FNAC REPORT)*

(1) **Non diagnostic or Unsatisfactory**

Cyst fluid only Acellular specimen Other (obscuring blood, clotting artifact, etc)

(2) Benign

Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc)

Consistent with lymphocytic (Hashimoto) thyroiditis

Consistent with granulomatous (subacute) thyroiditis

others

(3) Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance

(4)Follicular Neoplasm or Suspicious for a Follicular Neoplasm

Hürthle cell (oncocytic) type

(5) Suspicious for Malignancy

Suspicious for papillary carcinoma Suspicious for medullary carcinoma

Suspicious for metastatic carcinoma Other

(6) Malignant

Papillary thyroid carcinoma Poorly differentiated carcinoma Medullary thyroid carcinoma

Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma

Carcinoma with mixed features: follicular variant of papillary

Metastatic carcinoma Non-Hodgkin lymphoma

Other

ULTRA SOUND ASSESSMENT:

Punctate microcalcifications (1) Y (0)N Hypoechogenicity (1) Y (0)N

Irregular margins or no halo (1) Y (0) N Solid (1)Y (0)N

Cystic (1)Y (0)N Mixed (1)Y (0)N

Intranodule vascularity (1)Y (0)N More tall than wide (1)Y (0)N

Lymph Node / Cystic (1)Y (0)N Size

HISTOPATHOLOGY:

Malignant: (1) y (0) n

Papillary thyroid carcinoma Poorly differentiated carcinoma Medullary thyroid carcinoma

Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma

Carcinoma with mixed features (specify) Metastatic carcinoma

Non-Hodgkin lymphoma Nodular with carcinoma Hashimoto's with carcinoma

BENIGN:

nodular Cyst Hashimoto's

CONSENT:

I understand that I am taking part in a research study on thyroid nodules. My participation in the study if until I get my final histopathology report after surgery. Taking part in this study does not involve any tests other than which I would normally undergo as a part of evaluation of my thyroid nodule. The risks and unforeseen complications of taking part in this study is the same as any other non study patient. I also understand that my records will be kept confidential and only the author of this study will have access to it. My participation is voluntary, and i can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefit.

All of the above has been explained to me in my own language.

Sign: Doctor's sign:

Name of doctor:

Bibliography:

1. Evaluation of a thyroid nodule Steven R. Bomeli, MD1, Shane O. LeBeau, MD2, and Robert L Ferris, MD, PhD1 1 University of Pittsburgh, Department of Otolaryngology, Head & Neck Surgery, Pittsburgh, PA 2 University of Pittsburgh, Division of Endocrinology and Metabolism, Pittsburgh, PA.

2. Revised American Thyroid Association Management Guidelines for Patients with Thyroid odules and Differentiated Thyroid Cancer The American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer David S. Cooper, M.D.1 (Chair)*, Gerard M. Doherty, M.D.,2 Bryan R. Haugen, M.D.,3 Richard T. Kloos, M.D.,4 Stephanie L. Lee, M.D., Ph.D.,5 Susan J. Mandel, M.D., M.P.H.,6 Ernest L. Mazzaferri, M.D.,7 Bryan McIver, M.D., Ph.D.,8 Furio Pacini, M.D.,9 Martin Schlumberger, M.D.,10 Steven I. Sherman, M.D.,11 David L. Steward, M.D.,12 and R. Michael Tuttle, M.D.13.

3. Thyroid Nodule Size Larger Than 4 cm Does Not Increase the Risk of False Negative FNA Cytology or the Risk of Malignancy Burch HB, Shrestha M, Crothers BA. The impact of thyroid nodule size on the risk of malignancy and accuracy of fine-needle aspiration: a ten-year study from a single institution. Thyroid September 10, 2012.

4. Surgical Management ofWell -Differentiated Thyroid Cancer: State of the Ar t James Suliburk, MDa, Leigh Delbridge, MD, FRACSb,*surgical clinics of north america 2009.

5. American thyroid assiciation of clinicak OF CLINICAL ENDOCRINOLOGISTS AND ASSOCIAZIONE MEDICI ENDOCRINOLOGI MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE DIAGNOSIS AND MANAGEMENT OF THYROID NODULES.

6. CONTINUING MEDICAL EDUCATION SOLITARY THYROID NODULE: CURRENT MANAGEMENT LEIGH DELBRIDGE University of Sydney, Endocrine Surgical Unit, Department of Surgery, Royal North Shore Hospital, Sydney, New South Wales, Australia.

7. Mary C. Frates. Management of Thyroid Nodules Detected at US: Society of Radiologists in Ultrasound Consensus Conference Statement1.

8. Rago T, Vitti P. Role of thyroid ultrasound in the diagnostic evaluation of thyroid nodules. Best Pract. Res. Clin. Endocrinol. Metab. 2008 Dec;22(6):913–28.

9. Ultrasound of Thyroid Nodules Terry S. Desser, MD*, Aya Kamaya, MD.

10. Panagiotis Touzopoulos1 Michael Karanikas1 Paul Zarogoulidis2 Alexandros Mitrakas1 Konstantinos Porpodis2 Nikolaos Katsikogiannis3 Vasilis Zervas2 Ioannis Kouroumichakis4 Theodoros C Constantinidis5 Dimitrios Mikroulis6 Konstantinos E Tsimogiannis7 1First Surgery Department. Journal of Multidisciplinary Healthcare Current surgical status of thyroid diseases.

11. Midwest Surgical Association False-negative fine-needle aspiration of thyroid nodules cannot be attributed to sampling error alone Xiao-Min Yu, M.D., Ph.D., Priyesh N. Patel, B.S., Herbert Chen, M.D., F.A.C.S., Rebecca S. Sippel, M.D., F.A.C.S.*.

12. AJCP / Special Article The Bethesda System for Reporting Thyroid Cytopathology Edmund S. Cibas, MD,1 and Syed Z. Ali, MD2.

13. http://www.uptodate.com/contents/thyroid-biopsy?source=search_result&search=fine+needle+aspiration&selectedTitle=6~150.

14. Wu HH-J, Rose C, Elsheikh TM. The Bethesda system for reporting thyroid cytopathology: An experience of 1,382 cases in a community practice setting with the implication for risk of neoplasm and risk of malignancy. Diagn. Cytopathol. 2012 May;40(5):399–403.

15. thyroidmanager.org/chapter/thyroid-cancer.

16. Nayar R, Ivanovic M. The indeterminate thyroid fine-needle aspiration: experience from an academic center using terminology similar to that proposed in the 2007 National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference. Cancer. 2009 Jun 25;117(3):195–202.

17. Iain J. Nixon. Nomogram for predicting malignancy in thyroid nodules using clinical, biochemical, ultrasonographic, and cytologic features.

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

Dr.B.J.Prashanthum, M.A.,M.A.,Dr.Min(Clinical)
Director, Christian Counseling Centre
Editor, Indian Journal of Psychological Counseling
Chairperson, Ethics Committee, IRB

Dr. Alfred Job Daniel, MS Ortho
Chairperson, Research Committee &
Principal

Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

November 22, 2012

Dr. Vimalin Samuel
Department of Surgery
Christian Medical College
Vellore 632 004

Sub: **FLUID Research grant project NEW PROPOSAL:**
A scoring system for clinical assessment of thyroid nodules.
Dr. Vimalin Samuel, Surgery, Dr. M.J. Paul Surgery, Dr. Elsa Chrispal, Dr. Aparna I, Radiology, Dr. Anu Jacob, Pathology.

Ref: IRB Min. No. 7341 dated 17.11.2010

Dear Dr. Samuel,

The Institutional Review Board (Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "A scoring system for clinical assessment of thyroid nodules" on November 17, 2010.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Informed Consent Form and Patient Information sheet (English, Tamil, Hindi and Bengali)
3. A CD containing document 1 – 3

The following Ethics Committee members were present at the meeting held on November 17, 2010 at 10:00 am in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. Prabhakar D Moses (on behalf of Dr. Lionel Gnanaraj)	MBBS, MS, M.Ch. (Urol)	Medical Superintendent, CMC.	
Mrs. Mary Johnson	M.Sc. (Nursing)	Addl. Nursing Superintendent, CMC.	
Mrs. Shirley David	M.Sc. (Nursing), RN RM	Addl. Deputy Dean, College of Nursing, CMC.	
Rev. Malhia Joshua	MA, MEd, MTh, PhD	Chaplain, CMC	

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

Dr.B.J.Prashantham, M.A.,M.A.,Dr.Min(Clinical)
Director, Christian Counseling Centre
Editor, Indian Journal of Psychological Counseling
Chairperson, Ethics Committee, IRB

Dr. Alfred Job Daniel, MS Ortho
Chairperson, Research Committee &
Principal

Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Mr. Harikrishnan	BL.	Lawyer	External
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M.Phil, BL.	Legal Advisor, CMC.	
Dr. Srinivas Babu	MSc, Ph.D.	Sr. Scientist, Neurological Sciences, CMC.	
Mrs. S. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External
Dr. P. Zachariah	MBBS, PhD	Retired Professor , Vellore	External
Dr. Gagandeep Kang	MD, PhD, FRCPath.	Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Microbiology & Addl. Vice Principal (Research), CMC.	

We approve the project to be conducted in its presented form.

The Institutional Ethics Committee / Independent Ethics Committee expects to be informed about the progress of the project, any SAE occurring in the course of the project, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

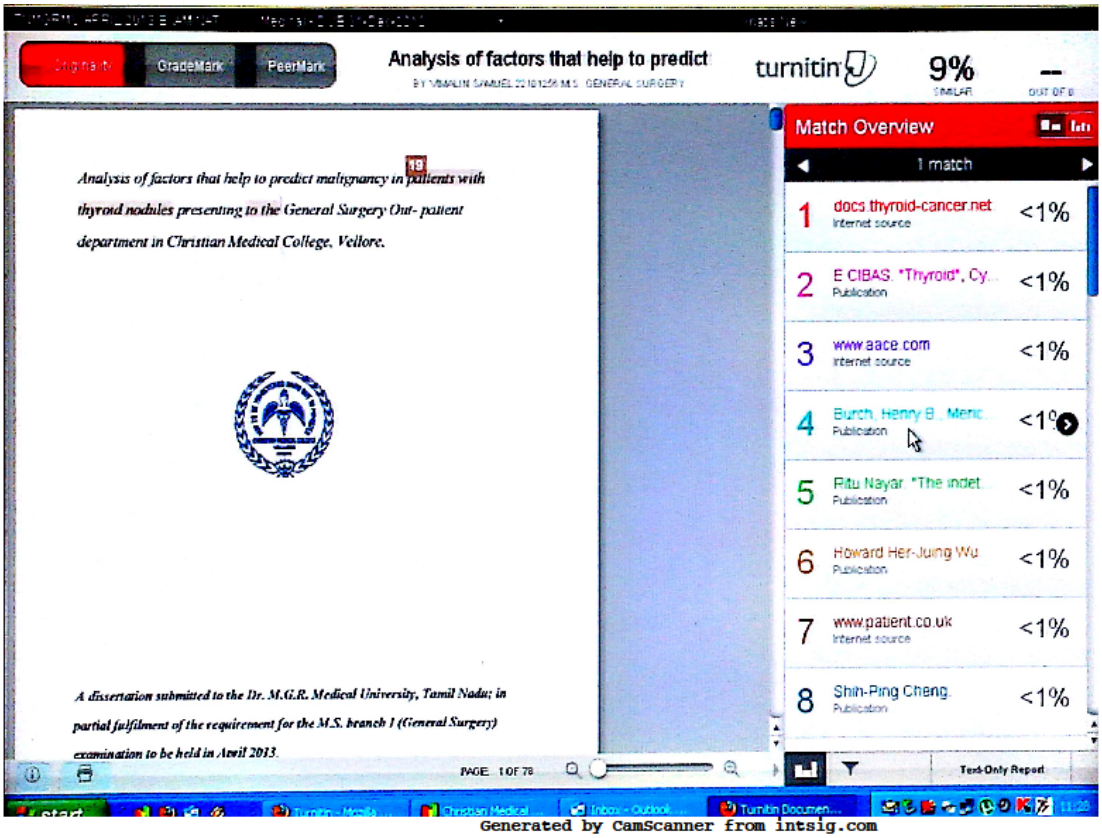
A sum of ₹ **36,920**/- (Rupees Thirty six thousand nine hundred and twenty only) is sanctioned for 2 years.

Yours sincerely,

Dr. Alfred Job Daniel
Principal & Chairperson (Research Committee)
Institutional Review Board

Chairperson (Research Committee) &
Principal
[illegible]tian Medical College
[illegible] 632 002, Tamil Nadu, India

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in



INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

Dr.B.J.Prashantham, M.A.,M.A.,Dr.Min(Clinical)
Director, Christian Counseling Centre
Editor, Indian Journal of Psychological Counseling
Chairperson, Ethics Committee, IRB

Dr. Alfred Job Daniel, MS Ortho
Chairperson, Research Committee &
Principal

Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

November 22, 2012

Dr. Vimalin Samuel
Department of Surgery
Christian Medical College
Vellore 632 004

Sub: **FLUID Research grant project NEW PROPOSAL:**
A scoring system for clinical assessment of thyroid nodules.
Dr. Vimalin Samuel, Surgery, Dr. M.J. Paul Surgery, Dr. Elsa Chrispal, Dr. Aparna I, Radiology, Dr. Anu Jacob, Pathology.

Ref: IRB Min. No. 7341 dated 17.11.2010

Dear Dr. Samuel,

The Institutional Review Board (Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "A scoring system for clinical assessment of thyroid nodules" on November 17, 2010.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Informed Consent Form and Patient Information sheet (English, Tamil, Hindi and Bengali)
3. A CD containing document 1 – 3

The following Ethics Committee members were present at the meeting held on November 17, 2010 at 10:00 am in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. Prabhakar D Moses (on behalf of Dr. Lionel Gnanaraj)	MBBS, MS, M.Ch. (Urol)	Medical Superintendent, CMC.	
Mrs. Mary Johnson	M.Sc. (Nursing)	Addl. Nursing Superintendent, CMC.	
Mrs. Shirley David	M.Sc. (Nursing), RN RM	Addl. Deputy Dean, College of Nursing, CMC.	
Rev. Malhia Joshua	MA, MEd, MTh, PhD	Chaplain, CMC	

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

Dr.B.J.Prashantham, M.A.,M.A.,Dr.Min(Clinical)
Director, Christian Counseling Centre
Editor, Indian Journal of Psychological Counseling
Chairperson, Ethics Committee, IRB

Dr. Alfred Job Daniel, MS Ortho
Chairperson, Research Committee &
Principal

Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Mr. Harikrishnan	BL.	Lawyer	External
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M.Phil, BL.	Legal Advisor, CMC.	
Dr. Srinivas Babu	MSc, Ph.D.	Sr. Scientist, Neurological Sciences, CMC.	
Mrs. S. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External
Dr. P. Zachariah	MBBS, PhD	Retired Professor , Vellore	External
Dr. Gagandeep Kang	MD, PhD, FRCPath.	Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Microbiology & Addl. Vice Principal (Research), CMC.	

We approve the project to be conducted in its presented form.

The Institutional Ethics Committee / Independent Ethics Committee expects to be informed about the progress of the project, any SAE occurring in the course of the project, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

A sum of ₹ **36,920**/- (Rupees Thirty six thousand nine hundred and twenty only) is sanctioned for 2 years.

Yours sincerely,

Dr. Alfred Job Daniel
Principal & Chairperson (Research Committee)
Institutional Review Board

Chairperson (Research Committee) &
Principal
(tian Medical College
- 632 002, Tamil Nadu, India